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BENZENE DERIVATIVE OR PHARMACEUTICALLY ACCEPTABLE SALT THEREOF

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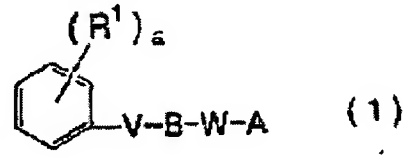
Abstract

Objective

To provide a novel compound that is excellent for suppressing collagen production.

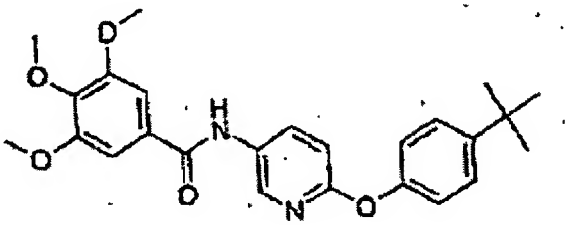
Means to Solve

A benzene derivative shown by the general formula (1):



(1)

concretely,

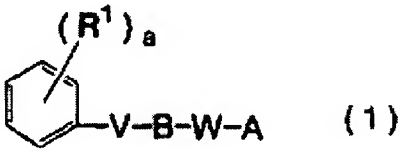


or a pharmaceutically acceptable salt thereof.

Claims

1. A benzene derivative shown by the general formula (1)

[Chemical formula 1]

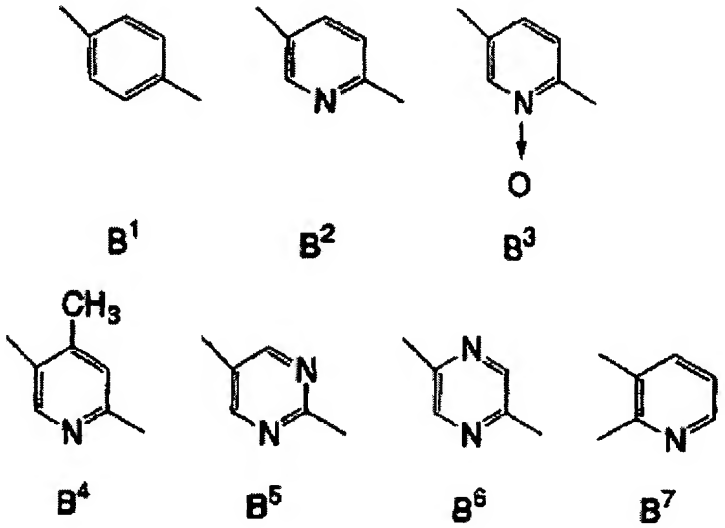


(1)

[wherein, R^1 are the same or different hydrogen atoms, halogen atoms, hydroxyl groups, nitro groups, cyano groups, carboxyl groups, lower alkoxycarbonyl groups, lower alkyl groups, halogen-substituted lower alkyl groups, lower alkoxy-substituted lower alkyl groups, hydroxy-substituted lower alkyl groups, carboxy-substituted lower alkyl groups, lower alkoxycarbonyl-

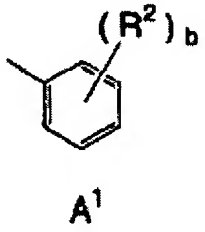
substituted lower alkyl groups, lower alkoxy groups, halogen-substituted lower alkoxy groups, lower alkyl group-substituted amino groups, or two adjacent groups joining together to form a 5- or 6-membered saturated or unsaturated hydrocarbon ring; a is an integer of 1-5; V is a group: -NHC(=O)-, the group: -C(=O)-NH-, the group: -NH-C(=O)-NH-, the group: -NH-C(=S)-NH-, the group: -S-CH_2-C(=O)-NH-, the group: -SO_2NH-, the group: -CH_2-NH-, the group: -CH_2NH-C(=O)-, the group: -C(=O)-N(CH_3)-, the group: -C(=O)-, group –CH_2-C(=O)-NH-, the group: -CH=CH-, the group: -O-CH_2-, the group: -CH_2CH_2-, the group: -N(CH_3CO)-C(=O)-, the group: -CH_2-C(=O)-, or group: -NH-C(=NH)-NH-; B is

[Chemical formula 2]



W is a group: -O-, the group: -S-, the group: -S(-O)-, the group: -NH-, the group: -C(=O)-, the group: -CH_2-, or group: -SO_2-; A is a group A^1:

[Chemical formula 3]

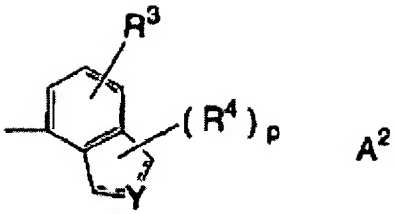


(wherein, R^2 are the same or different hydrogen atoms, lower alkyl groups, lower alkyl-substituted amino groups, lower alkanoyl groups, halogen atoms, 2-lower alkyl-1,3-dioxolane groups, lower alkoxycarbonyl groups, hydroxy-substituted lower alkyl groups, carboxyl groups, lower alkanoyloxy groups, lower alkanoyl-substituted lower alkyl groups, or two adjacent groups joining together to form a group:

[Chemical formula 4]

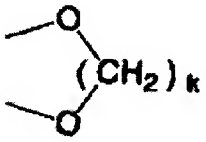
b is an integer of 1-5), group A^2:

[Chemical formula 5]



(wherein, R^3 is a hydrogen atom or lower alkyl group, R^4 are the same or different hydrogen atoms, hydroxyl groups, oxo groups, lower alkanoyloxy groups, alloyloxy groups, lower alkoxy groups, the group:

[Chemical formula 6]

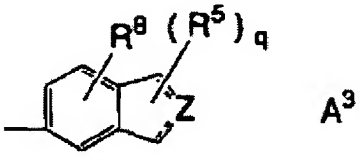


(wherein, k is an integer of 1-3), or group: =N-OR^6 (R^6 is a hydrogen atom, lower alkyl group, or lower alkanoyl group); p is an integer of 1-2;

[Chemical formula 7]

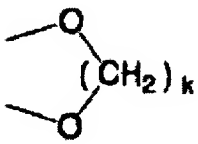
is a single bond or double bond; Y is a group: -$(CH_2)_m$-, the group: =$CH(CH_2)_{m-1}$, or group: -$(CH_2)_{m-1}$; m is an integer of 1-3), or groupA^3:

[Chemical formula 8]



(wherein, R^5 are the same or different hydrogen atoms, hydroxyl groups, oxo groups, lower alkanoyloxy groups, alloyloxy groups, lower alkoxy groups, the group:

[Chemical formula 9]



(wherein k is an integer of 1-3), or group: =N-OR^6 (R^6 is a hydrogen atom, lower alkyl group, or lower alkanoyl group); q is an integer of 1-2; R^8 is a hydrogen atom or lower alkyl group; [Chemical formula 10]

is a single bond or double bond; Z is a group: -$(CH_2)_n$-, the group: =$CH(CH_2)_{n-1}$-, or group: $(CH_2)_{n-1}CH$=, n is an integer of 1-3)] or a pharmaceutically acceptable salt thereof.

Detailed description of the invention

[0001]

Technological field of the invention

The present invention relates to a novel benzene derivative that inhibits collagen synthesis or a pharmaceutically acceptable salt thereof.

[0002]

Prior art

There are currently said to be more than 130 types of diseases called fibrosis, including rare diseases. Representative examples of diseases called fibrosis include pulmonary fibrosis, hepatic fibrosis, and glomerular sclerosis. In pulmonary fibrosis, the structure of the alveoli is generally destroyed by an inflammatory response. Proliferation of fibroblasts and an excessive increase in the extracellular matrix composed mainly of collagen occur as a result. The lung hardens and pulmonary function is lost due to reconstructive lesions in the region of the alveoli.

[0003]

Hepatic fibrosis is a condition in which hepatocytes are destroyed by a liver disorder such as chronic viral hepatitis or alcoholic liver dysfunction; the extracellular matrix increases in compensation in that location, and fibrosis develops in the liver. The final picture of this condition is complete atrophy of the liver tissue and hardening of the liver, leading to sclerosis of the liver. Penicillamine, which is known as a drug for the treatment of Wilkinson's disease caused by an accumulation of copper in the liver due to abnormal copper metabolism, and lufironil, which is being studied as a proline hydrogenase inhibitor, are used as drugs to treat hepatic fibrosis.

[0004]

Problems to be solved by the invention

These drugs, however, are not satisfactory as drugs to prevent hepatic fibrosis from standpoints such as adverse effects and the standpoint of efficacy. At the present point in time, there are no drugs (or treatment methods) that have been established to be effective in fibrosis as represented by hepatic fibrosis, and research is being conducted to determine whether there is some way to specifically inhibit the advance of fibrosis. As was mentioned above, excessive increases in the extracellular matrix composed mainly of collagen are implicated in the course of fibrosis in the lung tissue and hepatocytes. An increase in the extracellular matrix in the hepatocytes is also known to occur mainly in the Disse spaces in the sinusoidal walls, and the Ito cells, which are mesenchymal cells of the liver, are known to be the primary source of production.

[0005]

Suppressing the excessive increase in the extracellular matrix (i.e., collagen) therefore is important for suppressing fibrosis of the liver, lungs, and the like. The object of the present invention is thus to provide a novel compound that is excellent at suppressing collagen production.

[0006]

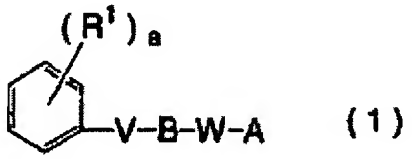
Means to solve the problems

As a result of in-depth research conducted to resolve the above problems, the present inventors obtained findings to the effect that benzene derivatives shown by the general formula (1) below and pharmaceutically acceptable salts thereof are excellent at suppressing collagen production and succeeded in perfecting the present invention.

General formula 1

[0007]

Chemical formula 11



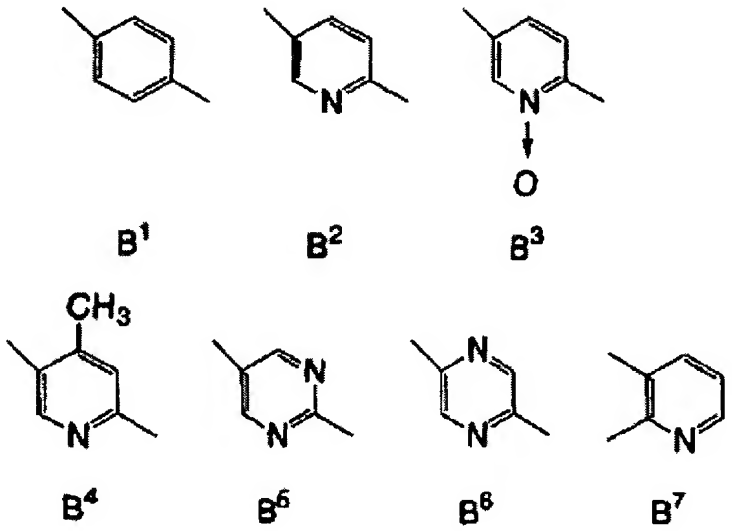
(1)

[0008]

[wherein, R^1 are the same or different hydrogen atoms, halogen atoms, hydroxyl groups, nitro groups, cyano groups, carboxyl groups, lower alkoxycarbonyl groups, lower alkyl groups, halogen-substituted lower alkyl groups, lower alkoxy-substituted lower alkyl groups, hydroxy-substituted lower alkyl groups, carboxy-substituted lower alkyl groups, lower alkoxycarbonyl-substituted lower alkyl groups, lower alkoxy groups, halogen-substituted lower alkoxy groups, lower alkyl group-substituted amino groups, or two adjacent groups joining together to form a 5- or 6-membered saturated or unsaturated hydrocarbon ring; a is an integer of 1-5; V is a group: -NHC(=O)-, the group: -C(=O)-NH-, the group: -NH-C(=O)-NH-, the group: -NH-C(=S)-NH-, the group: -S-CH_2-C(=O)-NH-, the group: -SO_2NH-, the group: -CH_2-NH-, the group: -CH_2NH-C(=O)-, the group: -C(=O)-N(CH_3)-, the group: -C(=O)-, group –CH_2-C(=O)-NH-, the group: -CH=CH-, the group: -O-CH_2-, the group: -CH_2CH_2-, the group: -N(CH_3CO)-C(=O)-, the group: -CH_2-C(=O)-, or group: -NH-C(=NH)-NH-; B is

[0009]

Chemical formula 12

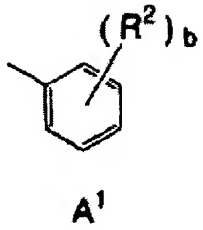


B^1 B^2 B^3 B^4 B^5 B^6 B^7

[0010]

W is a group: -O-, the group: -S-, the group: -S(-O)-, the group: -NH-, the group: -C(=O)-, the group: -CH_2-, or group: -SO_2-; A is a group A^1:

[0011]
Chemical formula 13

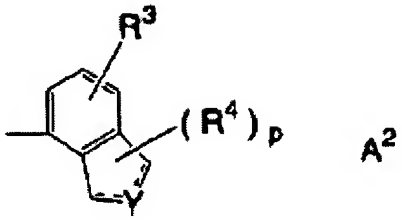


[0012]
(wherein, R^2 are the same or different hydrogen atoms, lower alkyl groups, lower alkyl-substituted amino groups, lower alkanoyl groups, halogen atoms, 2-lower alkyl-1,3-dioxolane groups, lower alkoxycarbonyl groups, hydroxy-substituted lower alkyl groups, carboxyl groups, lower alkanoyloxy groups, lower alkanoyl-substituted lower alkyl groups, or two adjacent groups joining together to form a group:

[0013]
Chemical formula 14

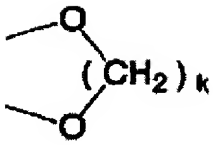
[0014]
b is an integer of 1-5), group A^2:

[0015]
Chemical formula 15



[0016]
(wherein, R^3 is a hydrogen atom or lower alkyl group, R^4 are the same or different hydrogen atoms, hydroxyl groups, oxo groups, lower alkanoyloxy groups, alloyloxy groups, lower alkoxy groups, the group:

[0017]
Chemical formula 16

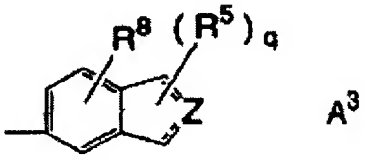


[0018]
(wherein, k is an integer of 1-3), or group: =N-OR^6 (R^6 is a hydrogen atom, lower alkyl group, or lower alkanoyl group); p is an integer of 1-2;

[0019]
Chemical formula 17

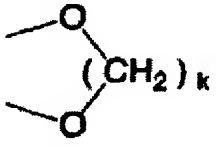
[0020]
is a single bond or double bond; Y is a group: -$(CH_2)_m$-, the group: =CH$(CH2)_{m-1}$, or group: -$(CH_2)_{m-1}$; m is an integer of 1-3), or group A^3:

[0021]
Chemical formula 18



[0022]
(wherein, R^5 are the same or different hydrogen atoms, hydroxyl groups, oxo groups, lower alkanoyloxy groups, alloyloxy groups, lower alkoxy groups, the group:

[0023]
[Chemical formula 19]



[0024]
(wherein k is an integer of 1-3), or group: =N-OR^6 (R^6 is a hydrogen atom, lower alkyl group, or lower alkanoyl group); q is an integer of 1-2; R^8 is a hydrogen atom or lower alkyl group;

[0025]
Chemical formula 20

[0026]
is a single bond or double bond; Z is a group: -$(CH_2)_n$-, the group: =$CH(CH_2)_{n-1}$-, or group: $(CH_2)_{n-1}CH$=, n is an integer of 1-3)] or a pharmaceutically acceptable salt thereof. The above benzene derivatives (1) and pharmaceutically acceptable salts thereof are excellent at suppressing collagen production, as was discussed above, and also have a long-lasting drug effect, good ability to circulate via the blood, and low toxicity.

[0027]
The benzene derivatives (1) and salts thereof of the present invention therefore are effective as drugs for the treatment of diseases associated with fibrosis caused by excessive collagen production, e.g. (i) organ diseases such as spontaneous and interstitial pulmonary fibrosis, pneumoconiosis, ARDS, hepatic fibrosis, neonatal hepatic fibrosis, sclerosis of the liver, purulent pancreatic fibrosis, and myelofibrosis, (ii) skin diseases such as scleroderma, elephantiasis, morphea, post-traumatic and post-operative hypertrophic scares, and keloids occurring after burns, (iii) vascular diseases such as atherosclerosis and arteriosclerosis, (iv) eye diseases such as diabetic retinopathy, posterior capsule fibrosis, neovascularization associated with corneal transplant, glaucoma, proliferative vitreous retinopathy, and post-operative corneal scarring, (v) kidney diseases such as atrophic nephropathy, renal sclerosis, renal fibrosis, interstitial nephropathy, IgA nephropathy, glomerular sclerosis, membranous nephritis, diabetic nephropathy, chronic interstitial nephritis, and chronic glomerulonephritis, and (vi) diseases of the bone or cartilage such as rheumatoid arthritis, chronic arthritis, and osteoarthritis.

[0028]
They are especially excellent at suppressing fibrosis associated with the diseases given as examples of organ diseases in (i) above, and are especially suited to the treatment of pulmonary fibrosis and hepatic fibrosis.

[0029]

Practical embodiment of the invention

The benzene derivatives shown by the above general formula (1) of the present invention include, for example, the following compounds.

1) Benzene derivatives, in which R^1, V, B, and W have the same definitions as in the above general formula (1) and A is a group A^2 or group A^3, and pharmaceutically acceptable salts thereof.

[0030]

2) Benzene derivatives, in which R^1, V, and B have the same definitions as in the above general formula (1), W is –O-, -S-, or –C(=O)-, and A is a group A^2 or group A^3, and pharmaceutically acceptable salts thereof.

3) Benzene derivatives, in which R^1, V, and B have the same definitions as in the above general formula (1), V is –NH-C(=O)-, -C(=O)-NH-, or –NH-C(=O)-NH-, and A is a group A^2 or group A^3, and pharmaceutically acceptable salts thereof.

[0031]

4) Benzene derivatives, in which R^1, V, W, and A have the same definitions as in the above general formula (1) and B is a group B^1, B^5, or B^6, and pharmaceutically acceptable salts thereof.

5) Benzene derivatives, in which R^1, V, W, and A have the same definitions as in the above general formula (1) and B is a group B^1, and pharmaceutically acceptable salts thereof.

6) Benzene derivatives, in which R^1, V, W, and A have the same definitions as in the above general formula (1) and B is a group B^5 or B^6, and pharmaceutically acceptable salts thereof.

[0032]

7) Benzene derivatives, in which A has the same definition as in the above general formula (1), R^1 is 3,4-dichloro, V is –C(=O)-HN-, B is a group B^1, W is –O-, and A is a group A^2 or A^3, and pharmaceutically acceptable salts thereof.

8) Benzene derivatives, in which R^1 is 4-trifluoromethyl, V is –CO-NH-, B is a group B^1, W is –O-, and A is a group A^2 or A^3, and pharmaceutically acceptable salts thereof.

[0033]

9) Benzene derivatives, in which A has the same definition as in the general formula (1) above, R^1 is 3,4-dichloro or 4-trifluoromethyl, V is –NH-C(=O)-, -C(=O)-NH-, or –NH-C(=O)-NH-, B is a group B^1, and W is –O-, -S-, or –C(=O)-, and pharmaceutically acceptable salts thereof.

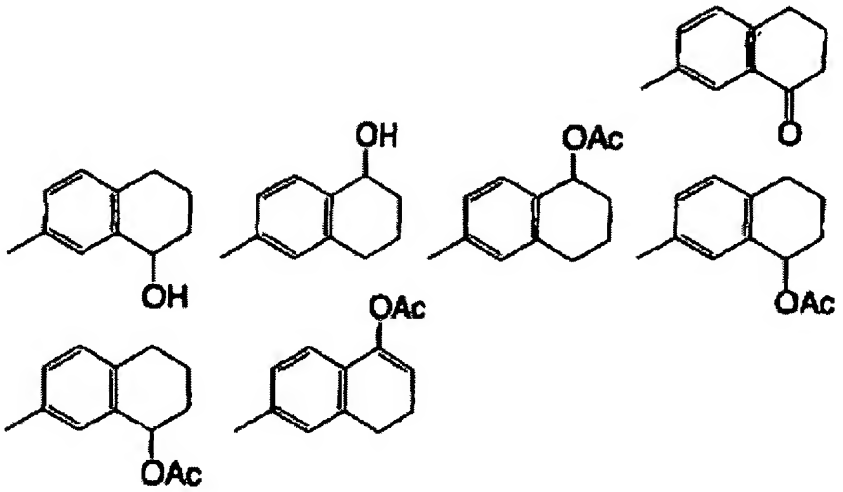
10) Benzene derivatives, in which R^1 is 3,4-dichloro or 4-trifluoromethyl, V is –NH-C(=O)-, -C(=O)-NH-, or –NH-C(=O)-NH-, B is a group B^1, W is –O-, -S-, or –C(=O)-, and A is a group A^2 or A^3, and pharmaceutically acceptable salts thereof.

[0034]

11) Benzene derivatives, in which R^1 is 3,4-dichloro or 4-trifluoromethyl, V is –C(=O)-NH-, B is a group B^1, W is –O-, and A is any group shown by

[0035]

Chemical formula 21



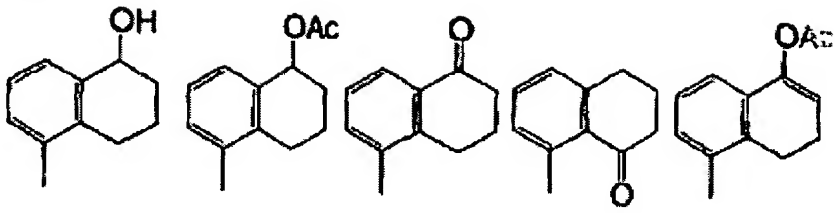
[0036]

(wherein, Ac is an acetyl group), and pharmaceutically acceptable salts thereof.

12) Benzene derivatives, in which R^1 is 3,4-dichloro or 4-trifluoromethyl, V is –C(=O)-NH-, B is a group B^1, W is –O-, and A is any group shown by

[0037]

Chemical formula 22



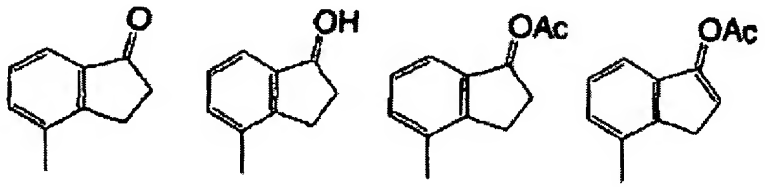
[0038]

and pharmaceutically acceptable salts thereof.

13) Benzene derivatives, in which R^1 is 3,4-dichloro or 4-trifluoromethyl, V is –C(=O)-NH-, B is a group B^1, W is –O-, and A is any group shown by

[0039]

Chemical formula 23



[0040]

and pharmaceutically acceptable salts thereof.

14) Benzene derivatives, in which R^1 is 2-methyl and 3,4-dichloro or 2-methyl and 4 trifluoromethyl, V is –C(=O)-NH-, B is a group B^1, W is –O-, and A is a group A^2 or A^3, and pharmaceutically acceptable salts thereof.

[0041]

15) Benzene derivatives, in which R^1 is 3,4-dichloro or 4-trifluoromethyl, V is -NH-C(=O)-NH-, B is a group B^6, W is –O-, and A is a group A^2 or A^3, and pharmaceutically acceptable salts thereof.

16) Benzene derivatives in which R^1 is 3,4-dichloro or 4-trifluoromethyl, V is –C(=O)-NH-, B is a group B^6, W is –O-, and A is a group A^2 or A^3, and pharmaceutically acceptable salts thereof.

[0042]

17) Benzene derivatives, in which R^1 is 3,4-dichloro or 4-trifluoromethyl, V is –C(=O)-NH- or –NH-C(=O)-NH-, B is a group B^2, W is –C(=O)-, and A is a group A^2 or A^3, and pharmaceutically acceptable salts thereof.

18) Benzene derivatives, in which R^1 is 3,4-dicyano, V is –C(=O)-NH- or –NH-C(=O)-NH-, B is a group B^1 or B^2, W is –O-, and A is a group A^2 or A^3, and pharmaceutically acceptable salts thereof.

[0043]

Each of the groups shown in the above general formula (1) will be explained concretely below. Examples of lower alkyl groups include linear or branched alkyl groups having 1-6 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, t-butyl, pentyl, and hexyl. Examples of hydroxy-substituted lower alkyl groups include hydroxy-lower alkyl groups in which the alkyl moiety is a linear or branched alkyl group having 1-6 carbon atoms such as hydroxymethyl, 2-hydroxyethyl, 1,1-dimethyl-2-hydroxyethyl, 3-hydroxypropyl, 4 hydroxybutyl, 2-hydroxybutyl, 5-hydroxypentyl, 1-hydroxypentyl, and 6-hydroxyhexyl.

[0044]

Examples of halogen-substituted lower alkyl groups include alkyl groups having 1-6 carbon atoms substituted by 1-3 halogen atoms such as monochloromethyl, monobromomethyl, monoiodomethyl, monofluoromethyl, dichloromethyl, dibromomethyl, diiodomethyl, difluoromethyl, trifluoromethyl, tribromomethyl, triiodomethyl, trifluoromethyl, monochloroethyl, monobromoethyl, monoiodoethyl, dichloroethyl, dibromoethyl, difluoroethyl, dichlorobutyl, diiodobutyl, difluorobutyl, chlorohexyl, bromohexyl, and fluorohexyl.

[0045]

Examples of 2-lower alkyl-1,3-dioxolane groups include 2-lower alkyl-1,3-dioxolane groups in which the alkyl moiety is an alkyl group having 1-6 carbon atoms such as 2-methyl-1,3-dioxolane, 2-ethyl-1,3-dioxolane, 2-propyl-1,3-dioxolane, 2-butyl-1,3-dioxolane, and 2 hexyl-1,3-dioxolane. Examples of halogen atoms are fluorine, chlorine, bromine, and iodine.

[0046]

Examples of the alkanoyl moiety of the lower alkanoyloxy groups and lower alkanoyl groups include linear and branched alkanoyl groups in which the alkyl moiety has 1-6 carbon atoms such as formyl, acetyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl,

pentanoyl, and hexanoyl. Examples of the alloyl moiety of the alloyloxy groups include benzoyl, toluoyl, naphthoyl, salicyloyl, anisoyl, and phenanthroyl.

[0047]

Examples of lower alkoxy groups include linear or branched alkoxy groups having 1-6 carbon atoms such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, pentyloxy, and hexyloxy. Examples of the hydrocarbon ring when two adjacent R^1 join together to form a 5- or 6-membered saturated or unsaturated hydrocarbon ring in the benzene derivatives of the above general formula (1) include a cyclopentane ring, cyclohexane ring, and cyclohexadiene ring.

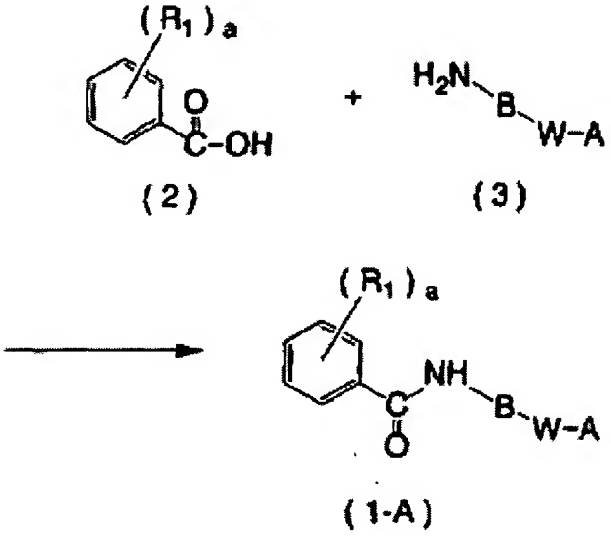
[0048]

The method of producing the benzene derivatives of the present invention is explained next.

Reaction scheme (I-a):

[0049]

Chemical formula 24



[0050]

(wherein, R^1, B, W, A, and a are the same as above.)

This reaction is a method that yields a benzene derivative (1-A) of the present invention in which V is –C(=O)-NH-. Specifically, the benzene derivative (1-A) is obtained by condensing a carboxylic acid (2) and 3-aminobenzene derivative (3) without a solvent or in an appropriate solvent using a water-soluble carbodiimide such as 1-ethyl-3-(3-

dimethylaminopropyl)carbodiimide hydrochloride or a carbodiimide such as N,N-dicyclohexylcarbodiimide (DCC) as the condensing agent.

[0051]

The addition of a tertiary amine improves the basicity of the amine compound (3) and accelerates the reaction. A condensing agent such as isobutyl chloroformate, diphenylphosphonic chloride, or carbonyl diimidazole may also be used instead of the above carbodiimides in the present invention. The solvent should be one that does not affect the reaction. Examples include inert solvents such as tetrahydrofuran (THF), N,N-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetonitrile, toluene, and 1,2-dimethoxyethane.

[0052]

Examples of the above tertiary amine include triethylamine, tributylamine, pyridine, N-methyl morpholine, quinoline, lutidine, and 4-dimethylaminopyridine. The amount of condensing agent used relative to compound (2) should be at least a 1-fold molar quantity, preferably a 1-5-fold molar quantity. The amount of the 3-amino compound (3) used relative to the compound (2) should be at least a 1-fold molar quantity, preferably a 1-5-fold molar quantity.

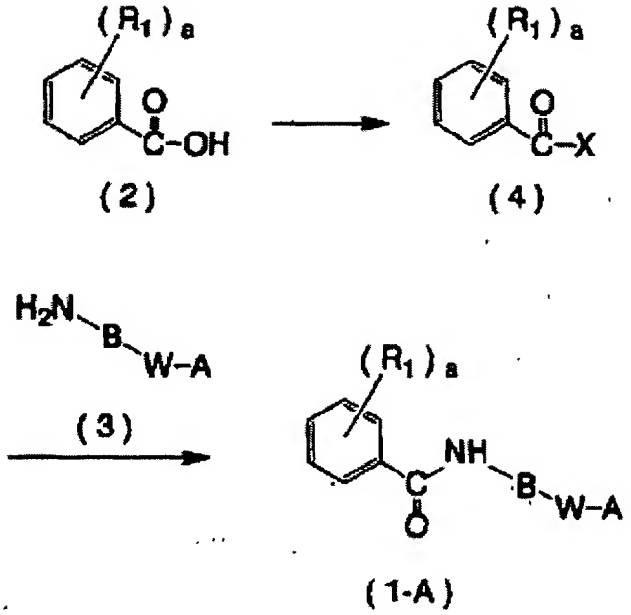
[0053]

The reaction is usually carried out at about -20 to 180°C, preferably 0-150°C, and is completed 5 min to 3 h after adding the condensing agent to the carboxylic acid (2) and 30 min to 30 h after adding the 3-amino compound (3).

Reaction scheme (I-b):

[0054]

Chemical formula 25



[0055]

(wherein, R^1, B, W, A, and a are the same as above; X is a halogen atom.) This reaction is another method of obtaining the above benzene derivative (1-A). Specifically, an acid halide (4) is obtained by reacting a carboxylic acid (2) with a halogenating agent without a solvent or in an appropriate solvent. The target product can then be obtained by reacting a 3-amino compound (3) with this acid halide (4). The addition of a tertiary amine removes the hydrogen halide from the reaction system and accelerates the reaction.

[0056]

Examples of the solvent used in this reaction include diethyl ether, tetrahydrofuran, dioxane, and other such ethers, methylene chloride, chloroform, dichloroethane, and other such halogenated hydrocarbons, benzene, toluene, and other such aromatic hydrocarbons, and dimethylformamide (DMF). Examples of the halogenating agent include thionyl chloride, thionyl bromide, and other such thionyl halides, hydrogen chloride, hydrogen bromide, hydrogen iodide, and other such hydrogen halides, and phosphorus trichloride, phosphorus tribromide, and other such phosphorus halides.

[0057]

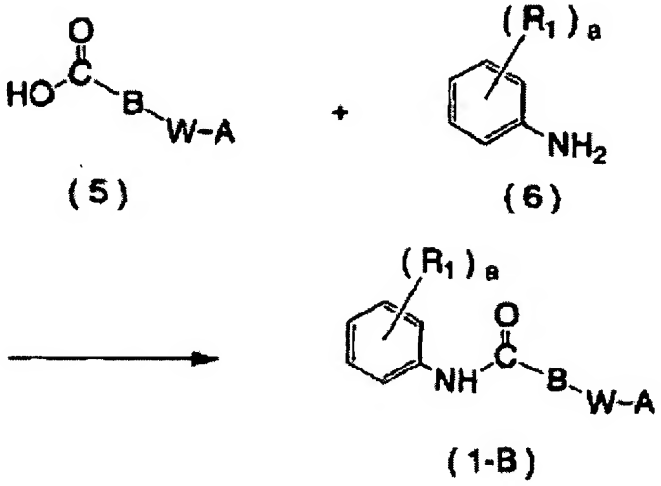
The amount of halogenating agent used relative to the carboxylic acid (2) is at least an equimolar quantity, preferably a 1-5-fold molar quantity. The amount of the 3-amino compound

(3) used relative to the acid halide (4) is at least an equimolar quantity, preferably a 1-5-fold molar quantity. The reaction is carried out at about -20 to 180°C, preferably 0-150°C, and is completed in 5 min to 30 h.

Reaction scheme (II):

[0058]

Chemical formula 26



[0059]

(wherein, R^1, B, W, A, and a are the same as above.)

This reaction is a method of obtaining a benzene derivative (1-B) of the present invention in which V is –NH-C(=O)-. Specifically, the benzene derivative (1-B) of the present invention is obtained by reacting a compound (5) and aniline derivative (6) in accordance with the method described in the above reaction scheme (I-a). Examples of the solvent, tertiary amine, and condensing agent used include those given as examples in the above reaction scheme (I-a).

[0060]

The amount of condensing agent used relative to the carboxylic acid compound (5) is at least a 1-fold molar quantity, preferably a 1-5-fold molar quantity. The amount of the aniline derivative (6) used relative to the carboxylic acid compound (5) is at least a 1-fold molar quantity, preferably a 1-5-fold molar quantity. The reaction is usually carried out at about -20 to 180°C, preferably 0-150°C, and is completed in 5 min to 3 h after adding the condensing agent to the pyridinecarboxylic acid (5) and from 30 min to 30 h after adding the aniline derivative (6).

[0061]

The benzene derivatives [1] and [2] below may be produced by reducing a benzene derivative (1-a) in which at least one of the R^4 is an oxo group or a benzene derivative (1-a') in which at least one of the R^6 is an oxo group among the benzene derivatives (1) of the present invention.

[1] Benzene derivative (1-b) in which Y in the group A^2 of the above A is a group: $-(CH_2)_m-$ and at least one of the R^4 is a hydroxyl group

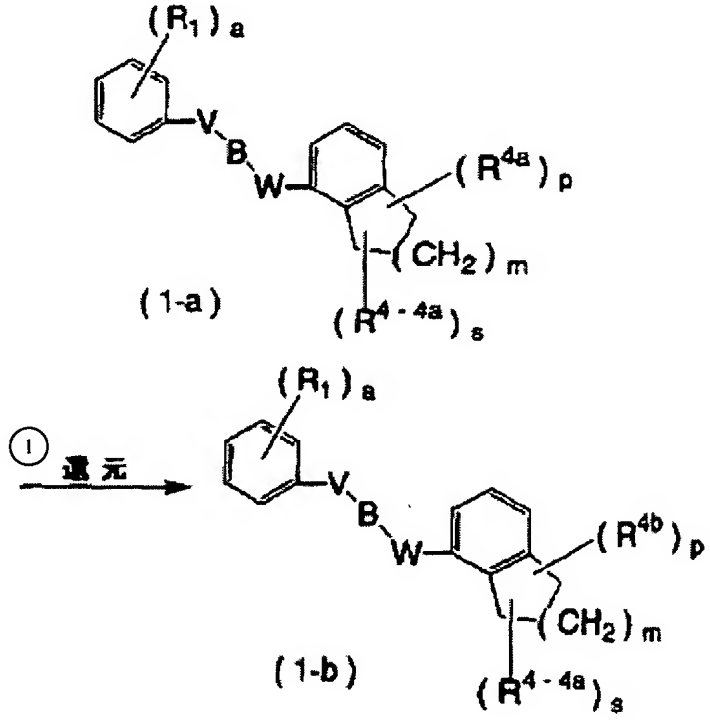
[2] Benzene derivative (1-b') in which Z in the group A^3 is $-(CH_2)_n-$ and at least one of the R^6 is a hydroxyl group.

For example, the benzene derivative (1-b) of [1] above is obtained by reducing the benzene derivative (1-a) in which at least one of the R^4 is an oxo group in an appropriate solvent as shown below in the reaction scheme (III-a).

Reaction scheme (III-a):

[0062]

Chemical formula 27



Key: 1 Reduction

[0063]

(wherein, R^1, V, B, W, a, p, and m are the same as above; R^{4a} is an oxo group; R^{4-4a} is a group with R^{4a} removed from the above R^4; s is 0 or 1; however, s is 0 when p is 2; R^{4b} is a hydroxyl group.) The solvent should be one that does not affect the reaction. Examples include tetrahydrofuran (THF), dioxane, diethyl ether, and other such ethers, methylene chloride, chloroform, and other such halogenated hydrocarbons, and benzene, toluene, and other such aromatic hydrocarbons.

[0064]

Examples of the method of reduction include catalytic reduction in an appropriate solvent and use of a reducing agent such as lithium aluminum hydride, sodium borohydride, lithium borohydride, diborane, or Raney nickel. The amount of reducing agent used relative to the benzene derivative (1-a) is usually a 1-5-fold molar quantity, preferably a 1-3-fold molar quantity, when there is one oxo group (R^{4a}) and usually a 2-10-fold molar quantity, preferably 2-6-fold molar quantity, when there are two oxo groups (R^{4a}). The reaction is usually carried out at 0-30°C and is completed in about 1-30 h.

[0065]

The derivative may also be produced using the benzene derivative (1-a) or (1-a') in which R^4 or R^5 is an oxo group as the starting material when R^4 in the group A^2 among the above A or R^5 in the group A^3 is a group: =N-OR^6 (R^6 is a hydrogen atom, lower alkyl group, or lower alkanoyl group) among the benzene derivatives (1) of the present invention. For example, a method of producing pyrimidine derivatives (1-f-1)-(1-f-3) in which R^6 in the group: =N-OR^6 is a hydrogen atom, lower alkyl group, or lower alkanoyl group will be explained sequentially, taking R^4 in the group A^2 as an example.

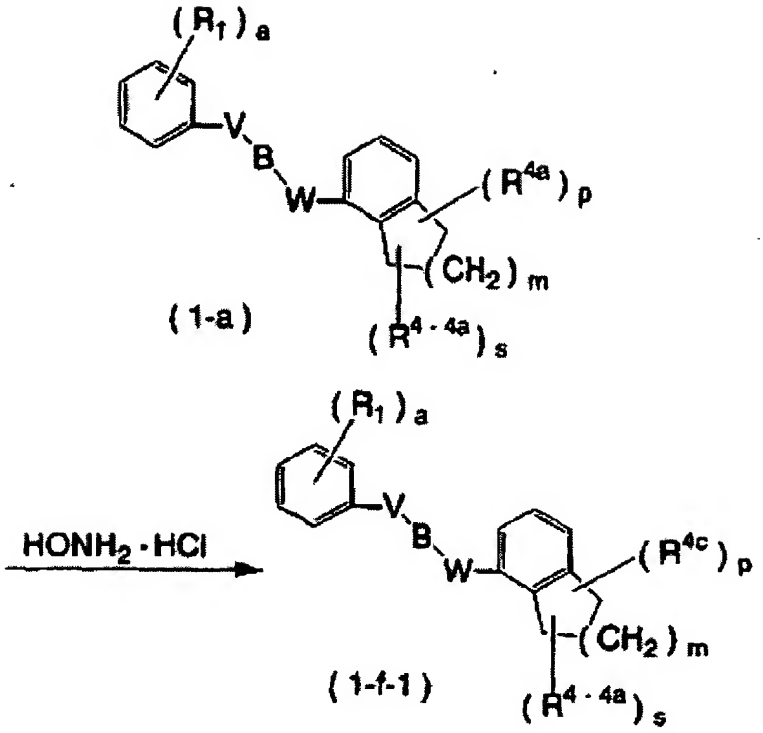
[0066]

First, a benzene derivative (1-f-1) in which R^4 is a group: =N-OH [sic; =N-OR^6] (R^6 is a hydrogen atom) is obtained by reacting the above benzene derivative (1-a) and a hydroxylamine hydrochloride salt in an appropriate solvent in the presence of a base as shown in the following reaction scheme (III-b).

Reaction scheme (III-b):

[0067]

Chemical formula 28



[0068]

(wherein, R^1, V, B, W, R^{4a}, R^{4-4a}, a, p, m, and s are the same as above; R^{4c} is a group: =N-OH.)

The solvent should be one that does not affect the reaction. Examples include tetrahydrofuran (THF), dioxane, diethyl ether, and other such ethers, methanol, ethanol, isopropanol, and other such lower alcohols, acetic acid, and water.

[0069]

Examples of the base include triethylamine and other such trialkylamines, potassium carbonate, barium carbonate, sodium carbonate, and other such alkali metal carbonates, sodium hydroxide, potassium hydroxide, and other such alkali metal hydroxides, and pyridine, 1,4-diazabicyclo[2.2.2]octane (DABCO), sodium acetate, and piperidine. The amount of base used is a 1-100-fold molar quantity, preferably 2-10-fold molar quantity, relative to the benzene derivative (1-a).

[0070]

The amount of hydroxylamine hydrochloride salt used relative to the benzene derivative (1-a) is a 1-50-fold molar quantity, preferably 2-10-fold molar quantity. The reaction is usually

carried out at -20 to 150°C and is completed in 5 min to 24 h. Benzene derivative (1 f-2) in which R^4 is a group: =N-OR^{6a} (R^{6a} is a lower alkyl group) can be produced by conducting the reaction in the same way as the method described in reaction scheme (III-b) using an O-alkylhydroxylamine hydrochloride salt instead of the above hydroxylamine hydrochloride salt.

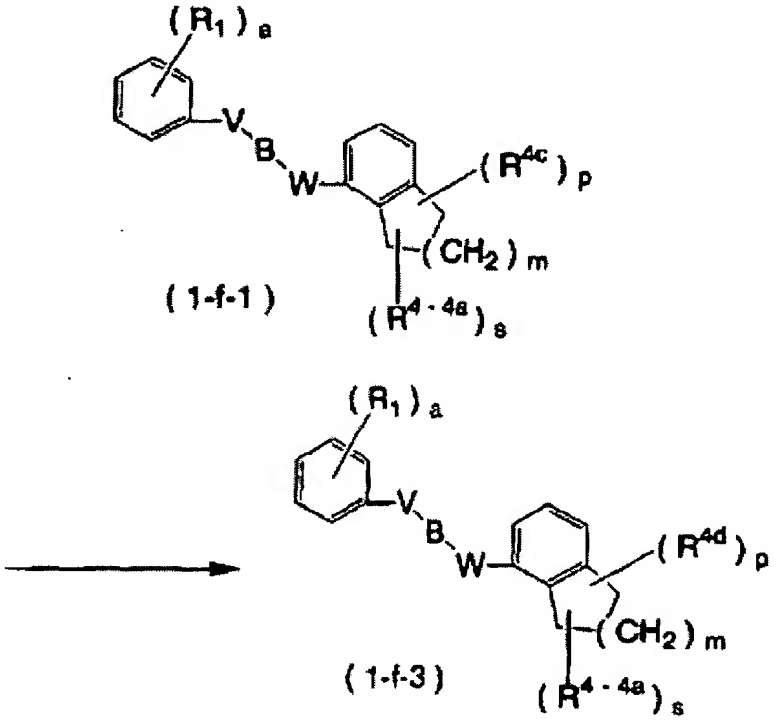
[0071]

For example, a benzene derivative (1-f-2) in which R^{6a} is a methyl group can be produced by reacting in the same way using an O-methyl hydroxylaminehydrochloride salt instead of the above hydroxylamine hydrochloride salt among the benzene derivatives (1-f-2). A benzene derivative (1-f-3) in which R^4 is a group: =N-OR^{6b} (R^{6b} is a lower alkanoyl group) is obtained by obtaining the benzene derivative (1-f-1) from the benzene derivative (1-a) in which R^4 is an oxo group in accordance with the method described in the above reaction scheme (III-b), then reacting this benzene derivative (1-f-1) with an acylating agent in an appropriate solvent as shown below in the reaction scheme (III-c). The addition of a tertiary amine accelerates the reaction because it heightens the basicity of the benzene derivative (1-f-1).

Reaction scheme (III-c):

[0072]

Chemical formula 29



[0073]

(wherein, R^1, V, B, W, R^{4c}, R^{4-4a}, a, p, m, and s are the same as above; R^{4d} is a group: =N-OR^{6b} (R^{6b} is the same as above.)

The solvent should be one that does not affect the reaction. Examples include tetrahydrofuran (THF), dioxane, diethyl ether, and other such ethers, methylene chloride, chloroform, and other such halogenated hydrocarbons, benzene, toluene, and other such aromatic hydrocarbons, and dimethylformamide.

[0074]

Examples of the above acylating agent include acid anhydrides and acid halides corresponding to the lower alkanoyl group of R^{6b}. Examples include acetic anhydride, acetyl halide, propionyl halide, isobutyryl halide, pivaloyl halide, and hexanoyl halide. To offer a concrete explanation, acetic anhydride or an acetyl halide such as acetyl chloride, acetyl fluoride, acetyl iodide, or acetyl bromide should be used as the acylating agent to obtain a benzene derivative (1-f-31) in which R^{6b} is an acetyl group.

[0075]

Examples of the tertiary amine include triethylamine and other such trialkylamines, pyridine, quinoline, lutidine, N-methylmorpholine, 4-dimethylaminopyridine, and imidazole. The amount of acylating agent used relative to the benzene derivative (1-f-1) is usually a 1-20-fold molar quantity, preferably 1-5-fold molar quantity, when there is one R^{4c} and usually a 2-40-fold molar quantity, preferably 2-10-fold molar quantity when there are two R^{4c}. The reaction is usually carried at -20 to 150°C and is completed in 5 min to 24 h.

[0076]

The pyrimidine derivatives (1-f'-1)-(1-f'-3) in which R^5 in the group A^3 is a group: =N-OR^6 (R^6 is the same as above) can also be produced by reacting in the same way as in the method described in the reaction scheme (III-b) using the benzene derivative (1-a') instead of the benzene derivative (1-a). The benzene derivatives [3]-[4] below among the benzene derivatives (1) of the present invention may also be produced by conducting dehydration in an appropriate solvent using a benzene derivative (1-g) in which Y in the group A^2 is a group: $(CH_2)_m$- and at least one of the R^4 is a hydroxyl group or a benzene derivative (1-g') in which Z in group A^3 is a group: -$(CH_2)_n$- and at least one of the R^5 is a hydroxyl group as the starting material.

[0077]

[3] Benzene derivative (1-c) in which Y in the group A^2 among the above A is a group: $=CH(CH_2)_{m-1}-$ or group: $-(CH_2)_m-1CH=$ and at least one of the R^4 is a hydrogen atom.

[4] Benzene derivative (1-c') in which Z in the group A^3 among the above A is a group: $=CH(CH2)_{n-1}-$ or group: $-(CH_2)_{n-1}CH=$ and at least one of the R^5 is a hydrogen atom.

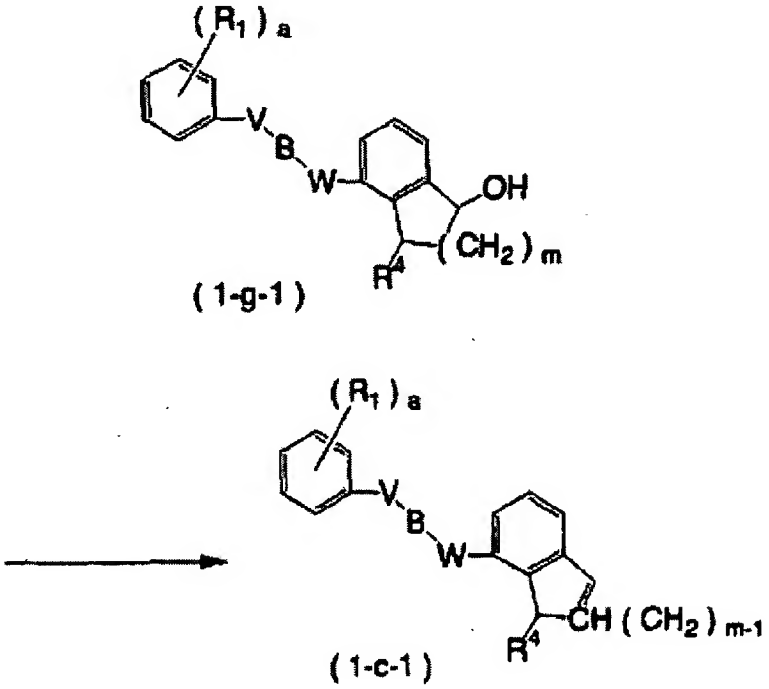
[0078]

This will be explained below using the method of synthesizing a benzene derivative (1-c) of [1] above as the example.

Reaction scheme (IV-a):

[0079]

Chemical formula 30



[0080]

(wherein, R^1, V, B, W, a, and m are the same as above.)

This reaction yields a benzene derivative (1-c-1) in which Y is a group: $-(CH_2)_{m-1}CH=$ by dehydrating the benzene derivative (1-g-1) that has hydroxyl groups in an appropriate solvent using a reagent such as pyridinium bromide perbromide, dioxane bromide, or bromine. The solvent should be one that does not affect the reaction. Examples include tetrahydrofuran (THF), dioxane, diethyl ether, and other such ethers, methylene chloride, chloroform, carbon

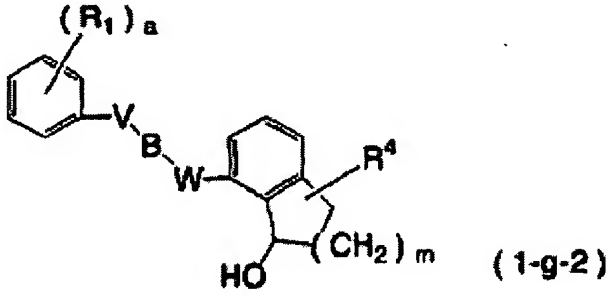
tetrachloride, and other such halogenated hydrocarbons, acetic acid, trifluoroacetic acid, and methanesulfonic acid.

[0081]

The amount of pyridinium bromide perbromide used relative to the benzene derivative (1-g-1) is usually a 1-5-fold molar quantity, preferably 1-3-fold molar quantity. The reaction is usually carried out at -10 to 150°C and is completed in about 30 min to 24 h. A benzene derivative (1-c-2) in which Y in the benzene derivative (1-c) of [1] above is a group: $=CH(CH_2)_{m-1}-$ can be produced by reacting in accordance with the method described in the reaction scheme (IV-a) using a benzene derivative of the general formula (1-g-2):

[0082]

Chemical formula 31



(1-g-2)

[0083]

(wherein, R^1, R^4, V, B, W, a, and m are the same as above) instead of the above benzene derivative (1-g-1). The benzene derivatives (1-d)-(1-e) and (1-d')-(1-e') shown in [5]-[8] below among the benzene derivatives (1) of the present invention may also be produced using a benzene derivative (1-h) in which Y in the group A^2 is a group: $-(CH_2)_m-$ and at least one of the R^4 is an oxo group or a benzene derivative (1-h') in which Z in the group A^3 is a group: $-(CH_2)_n-$ and at least one of the R^2 is an oxo group as the starting material.

[0084]

[5] Benzene derivative (1-d) in which Y in the group A^2 among the above A is a group: $=CH(CH_2)_{m-1}-$ or group: $-(CH_2)_{m-1}CH=$ and at least one of the R^4 is a lower alkanoyloxy group.

[6] Benzene derivative (1-d') in which Z in the group A^3 among the above A is a group: $=CH(CH_2)_{n-1}-$ or group: $-(CH_2)_{n-1}CH=$ and at least one of the R^5 is a lower alkanoyloxy group

[7] Benzene derivative (1-e) in which Y in the group A^2 among the above A is a group: $=CH(CH_2)_{m-1}-$ or group: $-(CH_2)_{m-1}CH=$ and at least one of the R^4 is a lower alkoxy group.

[8] Benzene derivative (1-e') in which Z in the group A^3 among the above A is a group: $=CH(CH_2)_{n-1}-$ or group: $-(CH_2)_{n-1}CH=$ and at least one of the R^5 is a lower alkoxy group.

The process for the production of the benzene derivatives (1-d)-(1-e) of [5] and [7] above will be explained using R^4 in the group A^2 as an example.

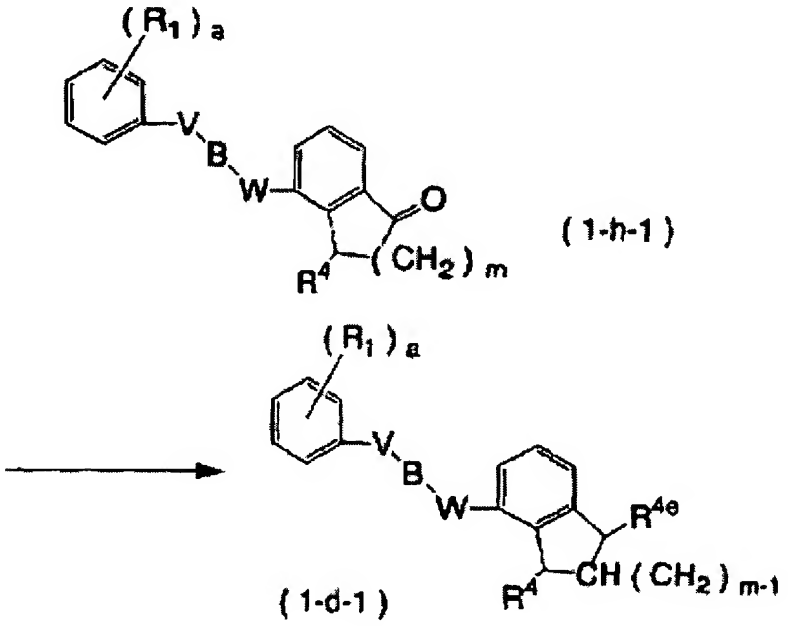
[0085]

The process for the production of the benzene derivative (1-d) of [5] above will be explained first using the following reaction scheme (IV-b).

Reaction scheme (IV-b):

[0086]

Chemical reaction 32



[0087]

(wherein, R^1, R^4, V, B, W, a, and m are the same as above; R^{4e} is a lower alkanoyloxy group.)

This reaction yields a benzene derivative (1-d-1) in which Y is a group: $-(CH_2)_{m-1}CH=$ and [sic] lower alkanoyloxy group by reacting a benzene derivative (1-h-1) that has oxo groups with an acylating agent without a solvent or in an appropriate solvent in the presence of an acid or base.

[0088]

The solvent should be one that does not affect the reaction. Examples include tetrahydrofuran (THF), dioxane, diethyl ether, and other such ethers, methylene chloride, chloroform, and other such halogenated hydrocarbons, benzene, toluene, and other such aromatic hydrocarbons, dimethylformamide, and acetic acid. Examples of the acylating agent include acid anhydrides, acid halides, and esters such as isopropenyl esters corresponding to the alkanoyl moiety of R^{4e}. Examples include acetic anhydride, acetyl halide, isopropenyl acetate, propionyl halide, isopropenyl propionate, isobutyryl halide, pivaloyl halide, and hexanoyl halide.

[0089]

To offer a concrete explanation, acetic anhydride, isopropenyl acetate, or an acetyl halide such as acetyl chloride, acetyl fluoride, acetyl iodide, or acetyl bromide should be used as the acylating agent to obtain the benzene derivative (1-d-11) in which R^{4e} is an acetyloxy group among the above benzene derivatives (1-d-1). Examples of the acid include boron trifluoride, boron trichloride, stannic chloride, titanium tetrachloride, boron trifluoride-ethyl ether complexes, zinc chloride, and other such Lewis acids, hydrogen chloride, hydrogen bromide, hydrogen fluoride, hydrogen iodide, and other such hydrogen halides, hydrochloric acid, hydrobromic acid, nitric acid, perchloric acid, sulfuric acid, and other such inorganic acids, trichloroacetic acid, trifluoroacetic acid, p-toluenesulfonic acid, and other such organic acids, and cation exchange resins.

[0090]

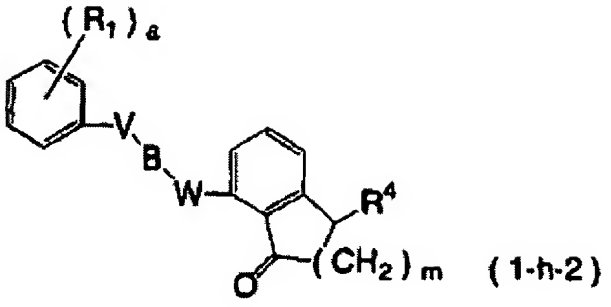
Examples of base include triethylamine and other such trialkylamines, pyridine, dimethylaminopyridine, lithium diisopropylamide (LDA), potassium hydride, sodium hydride, sodium methoxide, potassium acetate, sodium acetate, and anion exchange resins. The amount of acylating agent used relative to the benzene derivative (1-h-1) is usually a 1-100-fold molar quantity, preferably 2-5-fold molar quantity. The amount of acid or base used relative to the benzene derivative (1-h-1) is usually a 0.01-10-fold molar quantity, preferably 0.02-0.1-fold molar quantity. The reaction should usually carried out for from one min to 3 days, preferably 15 min to 24 h, at -78 to 150°C.

[0091]

A benzene derivative (1-d-2) in which Y in the benzene derivative (1-d) of [5] above is a group: $=CH(CH_2)_{m-1}-$ can also be produced by reacting in accordance with the method described in the reaction scheme (IV-b) using a benzene derivative shown by the general formula (1-h-2):

[0092]

Chemical formula 33



(1-h-2)

[0093]

(wherein, R^1, R^4, V, B, W, a, and m are the same as above) instead of the above benzene derivative (1-h-1). A benzene derivative (1-d') of [6] above can also be produced by reacting in the same way in accordance with the method described in the reaction scheme (IV-b) using a benzene derivative (1-h') in which at least one of the R^5 is an oxo group instead of the benzene derivative (1-h-1).

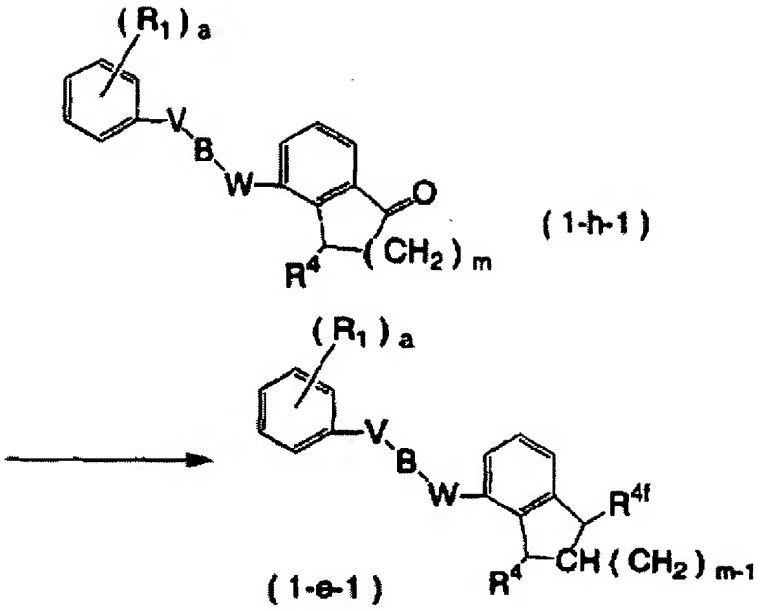
[0094]

The process of production of the benzene derivative (1-e) of [7] above will be explained next using the following reaction scheme (IV-c).

Reaction scheme (IV-c):

[0095]

Chemical formula 34



[0096]

(wherein, R^1, R^4, V, B, W, a, and m are the same as above; R^{4f} is a lower alkoxy group.)

This reaction yields a benzene derivative (1-e-1) that has lower alkoxy groups by reacting the above benzene derivative (1-h-1) and a lower alkyl ester of orthoformic acid in an appropriate solvent in the presence of an acid. Addition of anhydrous magnesium sulfate or molecular sieve 4A, and the like in this case facilitates the removal of water from the reaction system and accelerates the dehydration reaction.

[0097]

The solvent should be one that does not affect the reaction. Examples include tetrahydrofuran (THF), dioxane, diethyl ether, and other such ethers, methanol, ethanol, and other such lower alcohols, methylene chloride, chloroform, and other such halogenated hydrocarbons, benzene, toluene, and other such aromatic hydrocarbons, and nitromethane. Examples of the acid include boron trifluoride, boron trichloride, stannic chloride, titanium tetrachloride, boron trifluoride-ethyl ether complexes, zinc chloride, and other such Lewis acids, p-toluenesulfonic acid, trichloroacetic acid, trifluoroacetic acid, methanesulfonic acid, acetic acid, and (±)-10-camphorsulfonic acid.

[0098]

Examples of the lower alkyl esters of orthoformic acid include alkyl esters of orthoformic acid in which the alkyl moiety has 1-6 carbon atoms such as methyl orthoformate, ethyl orthoformate, butyl orthoformate, and hexyl orthoformate. To offer a concrete explanation, ethyl orthoformate should be used as the lower alkyl ester of orthoformic acid when obtaining a benzene derivative (1-e-11) in which R^{8f} is an ethoxy group among the above benzene derivatives (1-e-1).

[0099]

The amount of lower alkyl ester of orthoformic acid used relative to the benzene derivative (1-h-1) is usually a 1-100-fold molar quantity, preferably 5-20-fold molar quantity. The amount of acid used relative to the benzene derivative (1-h-1) is usually a 0.01-2-fold molar quantity, preferably 0.1-1.5-fold molar quantity. The reaction is usually carried out at -78 to 150°C and is completed in about 1 min to 24 h. A benzene derivative (1-e-2) in which Y in the above benzene derivatives (1-e) is a group: $=CH(CH_2)_{m-1}-$ can also be produced by reacting in the same way in accordance with the method described in reaction scheme (IV-c) using a benzene derivative (1-h-2) instead of the above benzene derivative (1-h-1).

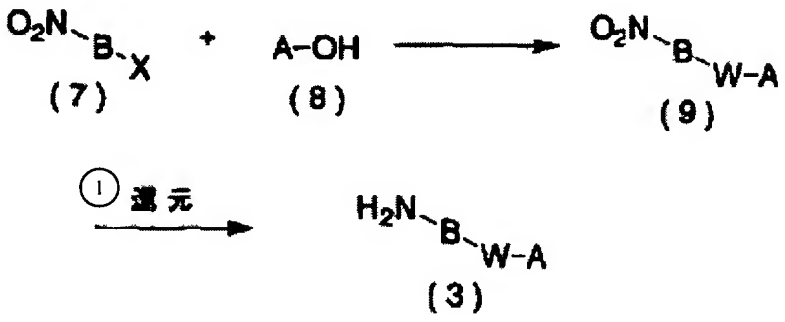
[0100]

A benzene derivative (1-e') of [8] above can also be produced by reacting in the same way in accordance with the method described in the reaction scheme (IV-c) using a benzene derivative (1-h') in which at least one of the R^5 is an oxo group instead of the benzene derivative (1-h-1).

Reaction scheme (V):

[0101]

Chemical formula 35



Key: 1 Reduction

[0102]

(wherein, B and A are the same as above.)

This reaction yields a compound (9) by reacting a monohalogenonitro derivative of B (7) with a compound (8). The above compound (3) that is a starting material of the reaction scheme (1-a) or reaction scheme (1-b) is then obtained by reducing this (9) by catalytic reduction in an appropriate solvent or by a catalyst such as zinc, iron, or tin in the presence of an acid.

[0103]

The reaction that yields the compound (9) from the monohalogenonitro compound (7) and compound (8) is carried out without a solvent or in an appropriate solvent. Potassium carbonate, sodium carbonate, or the like may be added to heighten the nucleophilicity of the compound (8). The reaction that yields the compound (9) may also be carried out without a solvent or in an appropriate solvent using alkali metal salts (such as sodium or potassium salts) of the monohalogenonitro compound (7) and compound (8).

[0104]

The solvent should be one that does not affect the reaction. Examples include methanol, ethanol, isopropanol, and other such lower alcohols, diethyl ether, tetrahydrofuran, dioxane, and other such ethers, methylene chloride, chloroform, and other such halogenated hydrocarbons, dimethylformamide, and dimethyl sulfoxide. The amount of the compound (8) used relative to the monohalogenobenzene derivative (7) is usually a 1-fold molar quantity, preferably 1-5-fold molar quantity.

[0105]

The reaction is usually carried out at 0-150°C, preferably 20-80°C and is completed in about 1-30 h. The reaction that yields the compound (3) from the compound (9) is carried out without a solvent or in an appropriate solvent. The solvent should be one that does not affect the reaction. Examples include methanol, ethanol, isopropanol, and other such lower alcohols, diethyl ether, tetrahydrofuran, dioxane, and other such ethers, dimethoxymethane, dimethoxyethane, and water.

[0106]

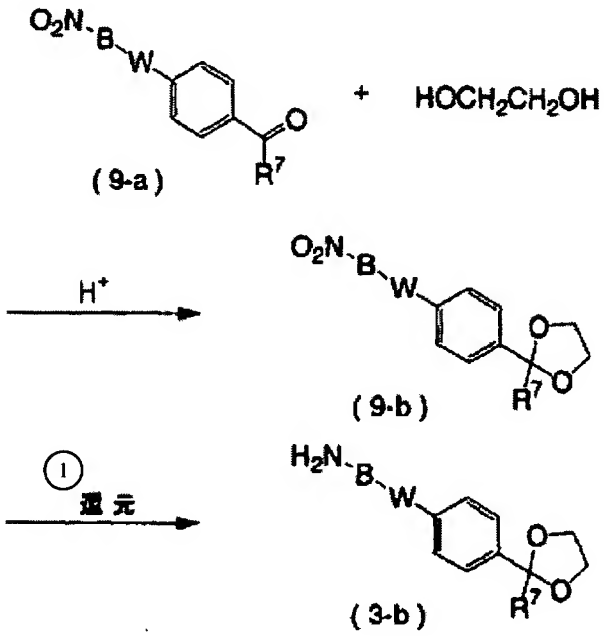
The amount of reducing agent used relative to the compound (9) is usually a 0.05-5-fold molar quantity, preferably 0.2-3-fold molar quantity. The reaction is usually carried out at 10 to

150°C, preferably 0-50°C, and is completed in about 30 min to 30 h. An aminobenzene derivative (3-b) in which two of the adjacent R^2 in the group A^1 of among the above A in the compound (3) join together to form a 2-lower alkyl-1,3-dioxolane group is synthesized according to the following reaction scheme (VI).

Reaction scheme (VI):

[0107]

Chemical formula 36



Key: 1 Reduction

[0108]

(wherein, R^7 is a lower alkyl group.)

Specifically, a cyclic acetal (dioxolane) compound (9-b) is obtained by reacting a nitro compound (9-a) with ethylene glycol in an appropriate solvent in the presence of an acid. The above aminobenzene derivative (3-b) is then obtained by reducing this compound (9-b) in the same way as in the above reaction scheme (III-a). The solvent should be one that does not affect the reaction. Examples include methanol, ethanol, isopropanol, and other such lower alcohols, diethyl ether, tetrahydrofuran, dioxane, and other such ethers, benzene, toluene, and other such aromatic hydrocarbons, and dimethoxyethane.

[0109]

Examples of the acid include p-toluenesulfonic acid, trichloroacetic acid, trifluoroacetic acid, methanesulfonic acid, acetic acid, and (±)-10-camphorsulfonic acid. The amount of ethylene glycol used relative to the nitro compound (9-a) is usually a 1-fold molar quantity, preferably 1-5-fold molar quantity. The amount of acid used relative to the nitro compound (9-a) is usually a 0.01-0.1-fold molar quantity, preferably 0.01-0.05-fold molar quantity.

[0110]

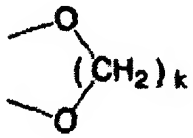
The reaction is usually carried out at -10 to 150°C, preferably from room temperature to 100°C, and is completed in about 1-30 h. A benzene derivative (1) of the present invention in which two adjacent R^2 in the group A^1 among the above A join together to form a 2-lower alkyl-1,3-dioxolane group may be produced in the present invention using an aminobenzene derivative (3-b) obtained by the above reaction scheme (VI) as the starting material or the oxo group may be converted into a cyclic acetal according to the methods described in the above reaction scheme (VI) after synthesizing a benzene derivative (1) in which two of the adjacent R^2 in the group A^1 among the above A are lower alkanoyl groups (however, excluding formyl groups).

[0111]

A benzene derivative (1) in which R^5 in the group A^3 among the above A is a group:

[0112]

Chemical formula 37



[0113]

(wherein, k is the same as above) can also be produced in the same way as in the case of R^2 in the group A^1 discussed above. The compounds (3-d)-(3-d') shown by (i)-(ii) below among the above compounds (3) may also be produced using a 3-nitrobenzene derivative (9-c) in which Y in the group A^2 is a group: $-(CHO_2)_m-$ and at least one of the R^4 is an oxo group or a 3 nitrobenzene derivative (9-c') in which Z in the group A^3 is $-(CH_2)_n-$ and at least one of the R^5 is an oxo group as the starting material.

(i) 3-Aminobenzene derivative (3-d) in which Y in the group A^2 among the above A is a group: $=CH(CH_2)_{m-1}-$ or a group: $-(CH_2)_{m-1}CH=$ and R^4 is a lower alkanoyloxy group.

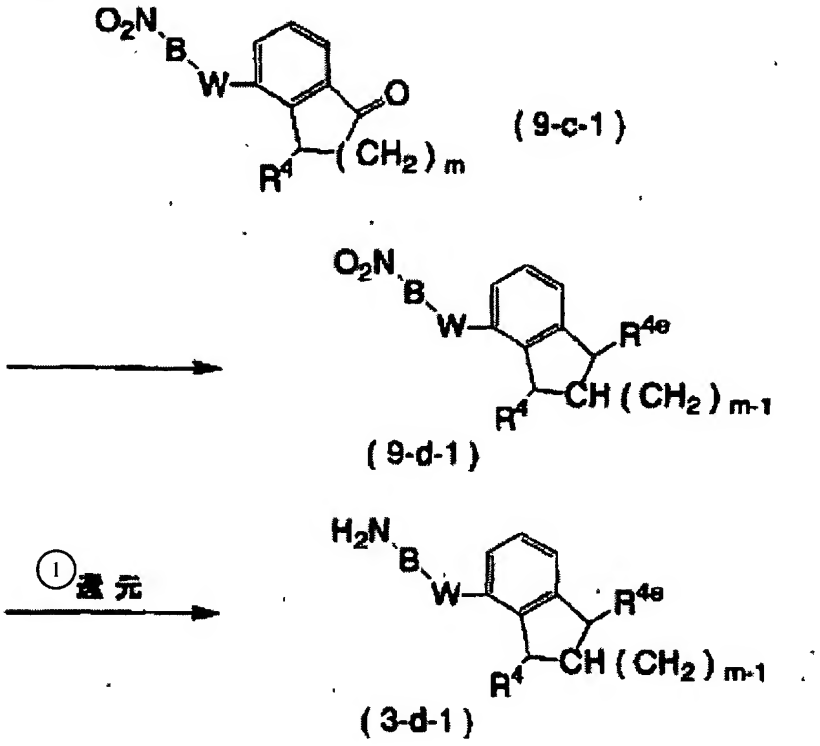
[0114]

(ii) 3-Aminobenzene derivative (3-d') in which Z in the group A^3 among the above A is a group: $=CH(CH_2)_{n-1}-$ or group: $-(CH_2)_{n-1}CH=$ and R^5 is a lower alkanoyloxy group.

This will be explained below taking the process for the production of a benzene derivative (3-d-1) in which Y in the group A^2 of (i) above is a group: $-(CH_2)_{m-1}CH=$ as an example. Reaction scheme (VII-a):

[0115]

Chemical formula 38



Key: 1 Reduction

[0116]

(wherein, R^4, m, and R^{4e} are the same as above.)

Specifically, as shown in the above reaction scheme (VII-a), the compound (3-d-1) is obtained by obtaining a 3-nitrobenzene derivative shown by the general formula (9-d-1) by reacting the above compound (9-c-1) with an acylating agent, then reducing this compound

(9-d-1) by reduction by a catalytic reduction method. The reaction that yields the compound (9 d-1) from the compound (9-c-1) is carried out without a solvent or in an appropriate solvent in the presence of an acid or base.

[0117]

The solvent should be one that does not affect the reaction. Examples include tetrahydrofuran (THF), dioxane, diethyl ether, and other such ethers, methylene chloride, chloroform, and other such halogenated hydrocarbons, benzene, toluene, and other such aromatic hydrocarbons, dimethylformamide, and acetic acid. An acid anhydride, acid halide, or ester such as an isopropenyl ester corresponding to the lower alkanoyl moiety of R^{4e} should be used as the acylating agent. To offer a concrete explanation, acetic anhydride, acetyl chloride, isopropenyl acetate, and the like should be used as the acylating agent (acetylating agent in this case) when obtaining a compound (3-d-11) in which R^{4e} is an acetyloxy group since the lower alkanoyl moiety of R^{4e} is acetyl.

[0118]

Examples of the acid include boron trifluoride, boron trichloride, stannic chloride, titanium tetrachloride, boron trifluoride-ethyl ether complexes, zinc chloride, and other such Lewis acids, hydrogen chloride, hydrogen bromide, hydrogen fluoride, hydrogen iodide, and other such hydrogen halides, hydrochloric acid, hydrobromic acid, nitric acid, perchloric acid, sulfuric acid, and other such inorganic acids, trichloroacetic acid, trifluoroacetic acid, p-toluenesulfonic acid, and other such organic acids, as well as cation exchange resins. Examples of the base include triethylamine and other such trialkylamines, pyridine, dimethylaminopyridine, lithium diisopropylamide (LDA), potassium hydride, sodium hydride, sodium methoxide, potassium acetate, sodium acetate, and anion exchange resins.

[0119]

The amount of acylating agent used relative to the compound (9-c-1) is usually a 1-100-fold molar quantity, preferably 2-5-fold molar quantity. The amount of acid or base used relative to the compound (9-c-1) is usually a 0.01-10-fold molar quantity, preferably 0.02-0.1-fold molar quantity. The reaction is usually carried out for 1 min to 3 days, preferably about 15 min to 24 h, at -78 to 150°C.

[0120]

The reaction that yields the compound (3-d-1) from the compound (9-d-1) is carried out in an appropriate solvent. The solvent should be one that does not affect the reaction. Examples

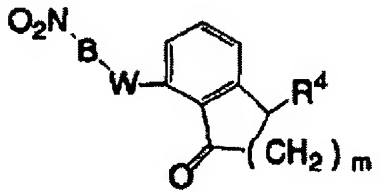
include tetrahydrofuran (THF), dioxane, and other such ethers, dimethoxyethane, diethoxyethane, and water. Examples of the reducing agent used in reduction include platinum dioxide, palladium-carbon (Pd-C), and Raney nickel. Platinum dioxide is especially excellent in selective reduction.

[0121]

The amount of reducing agent used relative to the compound (9-d-1) is usually a 0.01-5-fold molar quantity, preferably 0.02-0.1-fold molar quantity. The reaction is usually carried out at -10 to 150°C, preferably 0-50°C, and is completed in about 10 min to 30 h. A benzene derivative (3-d-2) in which Y in the compound (3-d) of (i) above is a group: $=CH(CH_2)_{m-1}-$ can be produced by reacting in the same way in accordance with the reaction scheme (VII-a) using a compound shown by the general formula (9-c-2):

[0122]

Chemical formula 39



(9-c-2)

[0123]

(wherein, R^4, B, W, and m are the same as above) instead of the compound (9-c-1). A compound (3-d') of (ii) above can also be produced by reacting in the same way in accordance with the reaction scheme (VII-a) using a compound (9-c') instead of the compound (9-c-1).

[0124]

The compounds (3-e)-(3-e') shown by (iii)-(iv) below among the above compounds (3) may be produced using a compound in which at least one of the R^4 is an acetyloxy group such as the compound (3-d-11) obtained by the above reaction scheme (VII-a) or the compounds (3 d'-11)-(3-d'-21) in which at least one of the R^5 is an acetyloxy group.

(iii) 3-Aminobenzene derivative (3-e) in which Y in the group A^2 among the above A is a group: $=CH(CH_2)_{m-1}-$ or group: $-(CH_2)_{m-1}CH=$ and at least one of the R^4 is an alloyloxy group.

[0125]

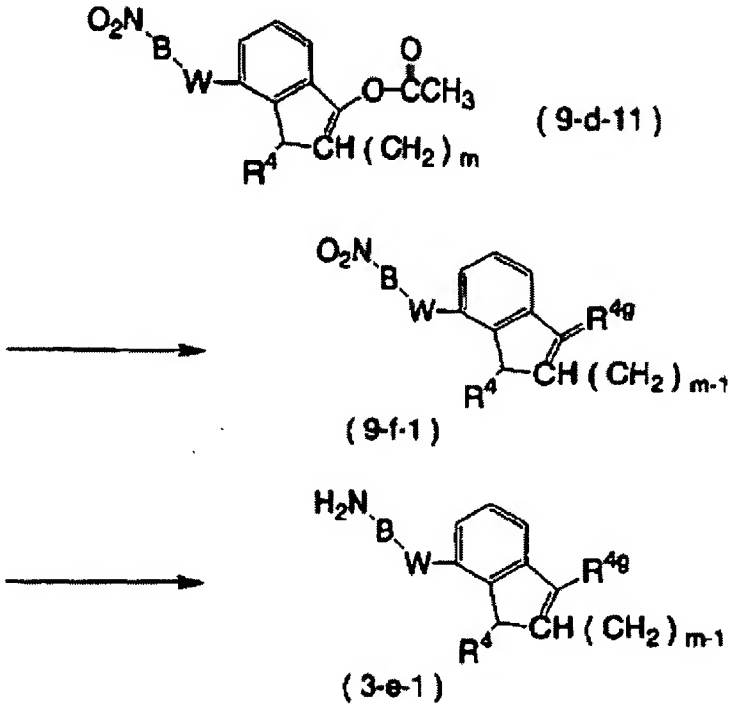
(iv) 3-Aminobenzene derivative (3-e') in which Z in the group A^3 among the above A is a group: $=CH(CH_2)_{n-1}-$ or group: $-(CH_2)_{n-1}CH=$ and at least one of the 5 is an alloyloxy group.

The process for the production of a 3-compound [sic] (3-e-1) in which Y in the group A^2 of (iii) above is a group: $-(CH_2)_{m-1}CH=$ will be explained here using the following reaction scheme (VI-b).

Reaction scheme (VII-b):

[0126]

Chemical formula 40



[0127]

(wherein, R^4, B, W, and m are the same as above; R^{4g} is an alloyloxy group.) This reaction yields a compound shown by the general formula (9-f-1) by reacting a compound (9-d-11) obtained by the reaction scheme (VII-a) with an acid-halogenating agent without a solvent or in an appropriate solvent, then obtains the compound (3-e-1) by reducing this compound (9-f-1) by a catalytic reduction method in the same way as in the above reaction scheme (VII-a).

[0128]

The solvent should be one that does not affect the reaction. Examples include tetrahydrofuran (THF), dioxane, diethyl ether, and other such ethers, carbon tetrachloride, methylene chloride, chloroform, and other such halogenated hydrocarbons, benzene, toluene, and other such aromatic hydrocarbons. An acid halide corresponding to the alloyl moiety of R^{4g} should be used as the acid halide. For example, a benzoyl halide such as benzoyl chloride, benzoyl bromide, benzoyl iodide, or benzoyl fluoride should be used to obtain a compound (3-e-11) in which the alloyl moiety of the alloyloxy groups is benzoyl.

[0129]

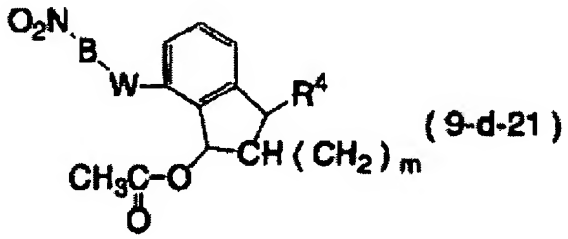
Examples of the acid include boron trifluoride, boron trichloride, stannic chloride, titanium tetrachloride, boron trifluoride-ethyl ether complexes, zinc chloride, and other such Lewis acids, hydrogen chloride, hydrogen bromide, hydrogen fluoride, hydrogen iodide, and other such hydrogen halides, hydrochloric acid, hydrobromic acid, nitric acid, perchloric acid, sulfuric acid, and other such inorganic acids, trichloroacetic acid, trifluoroacetic acid, p toluenesulfonic acid, and other such organic acids, as well as cation exchange resin. The amount of acid halide used relative to the compound (9-d-11) is usually a 1-100-fold molar quantity, preferably 5-10-fold molar quantity. The amount of acid or base used relative to the compound (9-d-11) is usually a 0.01-10-fold quantity, preferably 0.02-0.1-fold molar quantity. The reaction is usually carried out for 1 min to 3 days, preferably 15 min to 24 h, at -78 to 150°C.

[0130]

A benzene derivative (3-e-2) in which Y in the compound (3-e) of (iii) above is a group: $=CH(CH_2)_{m-1}-$ can also be produced by reacting in the same way in accordance with the method described in the reaction scheme (VII-b) using a benzene derivative shown by the general formula (9-d-21):

[0131]

Chemical formula 41



(9-d-21)

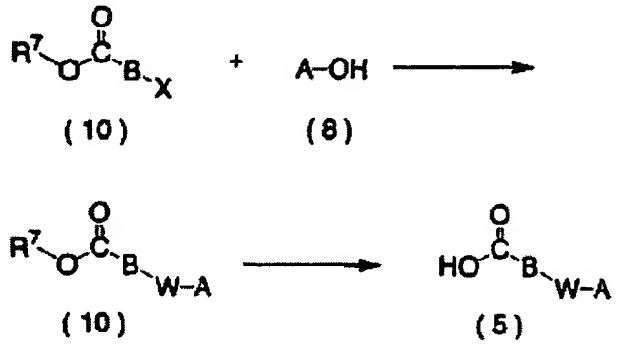
[0132]

(wherein, R^4, B, W, and m are the same as above) instead of the above benzene derivative (9-d-11). A compound (3-e') of (iv) above can also be produced by reacting in the same way in accordance with the method described in the above reaction scheme (VII-b) using a benzene derivative (9-d'-11) or (9-d'-21) in which A is a group: $=CH(CH_2)_{n-1}-$ or group: $-(CH_2)_{n-1}CH=$ and at least one of the R^5 is an acetyloxy group instead of the above benzene derivative (9-d-11).

Reaction scheme (VIII):

[0133]

Chemical formula 42



[0134]

(wherein, B, W, A, X, and R^7 are the same as above.)

This reaction yields a carboxylic acid ester derivative of B (11) by reacting a monohalogenocarboxylic acid ester of B (10) with a compound (8), and then yields the above carboxylic acid (5) that is a starting material of the reaction scheme (II) by hydrolyzing the protecting groups of the carboxyl groups in this compound (11). The reaction to obtain the pyridinecarboxylic acid ester derivative (11) from the monohalogenocarboxylic acid ester compound (10) may be carried out in the same way as in the above reaction scheme (V). The amount of the compound (8) used relative to the compound (10) is usually a 1-fold molar quantity, preferably 1-5-fold molar quantity. The reaction is usually carried out at 0-150°C, preferably 20-80°C, and is completed in about 1-30 h.

[0135]

The hydrolysis of the compound (11) is carried out in an appropriate solvent in the presence of a basic compound. Examples of this basic compound include sodium hydroxide, potassium hydroxide, and other such alkali metal hydroxides, sodium carbonate, potassium carbonate, and other such alkali metal carbonates, sodium bicarbonate, potassium bicarbonate,

and other such alkali metal bicarbonates, and other such inorganic bases, triethylamine, tributylamine, and other such trialkylamines, pyridine, picoline, 1,4-diazabicyclo[2.2.2]octane, and other such organic bases.

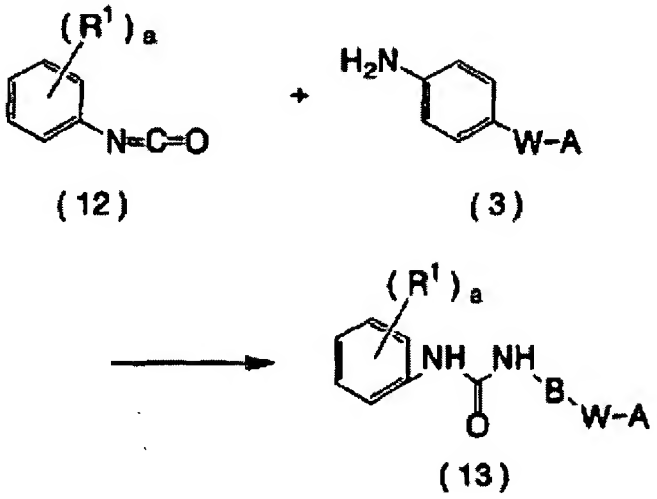
[0136]

The solvent should be one that does not affect the reaction. Examples include methanol, ethanol, isopropanol, and other such lower alcohols, diethyl ether, tetrahydrofuran, dioxane, and other such ethers, water, and their mixed solvents. The hydrolysis reaction is usually carried out at -10 to 200°C, preferably 30-60°C, and is completed in about 30 min to 24 h.

Reaction Scheme (IX):

[0137]

Chemical formula 43



[0138]

(wherein, R^1, B, W, A, and a have the same definitions as above.)

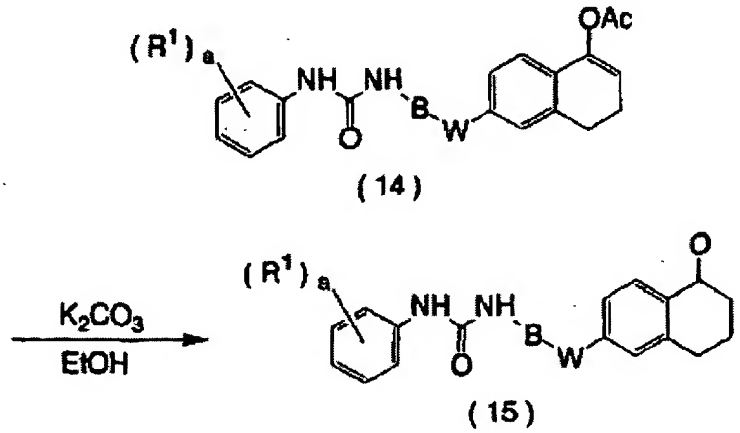
A benzene derivative (13) in which V in the general formula (1) is –NH-C(=O)-NH- is obtained by this reaction. An isocyanate compound (12) and a compound (3) are reacted without a solvent or in an inert solvent. Amines may be added to the system. Examples of the solvent include benzene, toluene, chlorobenzene, dichlorobenzene, acetone, and tetrahydrofuran. Examples of the amines include triethylamine, triisopropylamine, pyridine, and other such tertiary amines. The amount of amines used relative to the isocyanate compound (12) is usually a 1-5-fold molar quantity, preferably 1-2-fold molar quantity. The amount of the compound (3) used relative to the isocyanate compound (12) is usually a 1-10-fold molar quantity, preferably

1-3-fold molar quantity. The reaction is usually carried out at -10 to 150°C and is completed in about 10 min to 24 h.

Reaction scheme (X):

[0139]

Chemical formula 44



[0140]

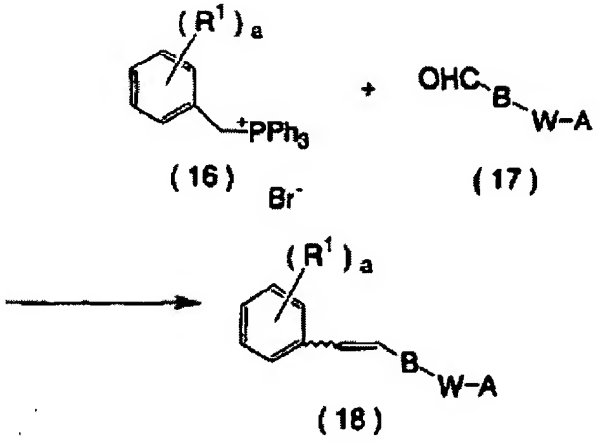
(wherein, R^1, B, W, A, and a have the same definitions as above.)

A compound (15) is obtained by this reaction by saponifying an enol ester derivative (14) in an appropriate solvent using an alkali. Examples of the alkali include alkali metal hydroxides or salts, alkaline-earth metal hydroxides or salts, and amines. A protic solvent can be used as the solvent. Examples include water, methanol, ethanol, and other such alcohols, tetrahydrofuran, dioxane, and other such ethers, acetonitrile, and dimethylformamide their or mixed solvents. The amount of alkali used is usually 1-10 mol, preferably 1-3 mol, per mol of the compound (14). The reaction is usually carried out at -10 to 150°C and is completed in approximately 30 min to 24 h.

Reaction scheme (XI):

[0141]

Chemical formula 45



[0142]

(wherein, R^1, B, W, A, and a have the same definitions as above.)

This reaction is a reaction to obtain a benzene derivative (18) in which V in the general formula (1) is –CH=CH-. The benzene compound (18) is obtained by this reaction by condensation (Wittig reaction) of a phosphorus ylide generated from a compound (16) and aldehyde compound (17). The phosphorus ylide is generated from the phosphonium salt (16) under anhydrous conditions by an appropriate combination of base-solvent. Examples of base-solvent combinations include sodium ethoxide-ethanol, N,N-dimethylformamide; sodium methoxide-methanol-ether, N,N-dimethylformamide; potassium t-butoxide-tetrahydrofuran, dichloromethane; n-butyllithium-ether, and phenyllithium-ether. The amount of base used is usually 1-10 mol, preferably 1-2 mol, per mol of the phosphonium salt (16). The reaction is usually carried out at -10 to 150°C and is completed in 30 min to 24 h. The reaction of the phosphorus ylide and aldehyde compound (17) is carried out in a solvent given as an example above. The amount of (16) used relative to (17) is usually a 1-10-fold molar quantity, preferably 1-3-fold molar quantity. The reaction is usually carried out at -10 to 150°C and is completed in form 30 min to 24 h.

[0143]

The benzene derivatives (1) of the present invention include pharmaceutically acceptable salts. Examples of such salts include hydrochlorides, hydrobromates, nitrates, sulfates, phosphates, and other such inorganic acid salts and methanesulfonates, p-toluene sulfonates, acetates, citrates, tartrates, maleates, fumarates, malates, lactates, and other such organic acid

salts. Medicinal preparations that contains the benzene derivatives (1) or pharmaceutically acceptable salts thereof of the present invention will be explained next.

[0144]

These medicinal preparations are the benzene derivatives (1) of the present invention made into ordinary medicinal preparation forms, prepared using commonly used diluents and excipients such as fillers, bulking agents, binders, humectants, disintegrating agents, and lubricants. Various forms can be selected as the medicinal preparation in accordance with the goal of treatment. Representative examples include tablets, pills, coarse granules, liquids, suspensions, emulsions, fine granules, capsules, suppositories, and injections (such as solutions and suspensions).

[0145]

A wide range of conventional, known carriers can be used when forming tablets. Lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, crystalline cellulose, silicic acid, and other such excipients, water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethylcellulose, shellac, methyl cellulose, potassium phosphate, polyvinylpyrrolidone, and other such binders, dry starch, sodium alginate, agar powder, laminaran powder, sodium bicarbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, stearic monoglyceride, starch, lactose, and other such disintegrating agents, sucrose, stearin, cocoa butter, hydrogenated oil, and other such disintegration inhibitors, quaternary ammonium base, sodium lauryl sulfate, and other such absorption accelerators, glycerin, starch, and other such humectants, starch, lactose, kaolin, bentonite, colloidal silicic acid, and other such adsorbents, refined talc, stearate, boric acid powder, polyethylene glycol, and other such lubricants can be used. The tablets can also be coated in ordinary ways if necessary. For example, sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, and double- or multi-layer-coated tablets can be made.

[0146]

A wide range of conventional, known carriers can be used when forming pills. Glucose, lactose, starch, cocoa butter, hydrogenated vegetable oil, kaolin, talc, and other such excipients, gum arabic powder, tragacanth powder, gelatin, ethanol, and other such binders, laminaran, agar, and other such disintegrating agents can be used. A wide range of conventional, known carriers can be used when forming suppositories. Polyethylene glycol, cocoa butter, higher alcohols, higher alcohol esters, gelatin, semisynthetic glycerides, and the like can be used.

[0147]

When preparing an injection, it is preferable to sterilize a solution, emulsion, or suspension and make it isotonic with the blood. A wide range of compounds used in the past as diluents can be used when forming the solution, emulsion, or suspension. Water, ethanol, propylene glycol, ethoxylated isostearyl alcohol, polyoxylated isostearyl alcohol, polyoxyethylene sorbitan fatty acid esters, and the like can be used. The medicinal preparation should also contain a sufficient amount of sodium chloride, glucose, or glycerin to prepare an isotonic solution in this case, and it may contain ordinary dissolution auxiliaries, buffers, analgesics, and, as needed, colorings, preservatives, fragrances, flavorings, sweeteners, and other drugs.

[0148]

The amount of benzene derivative (1) or salt thereof of the present invention contained in the medicinal preparation is not particularly restricted and can be selected from within a wide range. However, it is usually preferable that it be 1-70% by weight of the total composition. The method of administering the medicinal preparation of the present invention is not particularly restricted. It is administered in accordance with the type of preparation, patient's age, sex, disease condition, and other factors. For examples, tablets, pills, liquids, suspensions, emulsions, granules, and capsules are administered orally.

[0149]

An injection can be administered intravenously alone or mixed with an ordinary supplemental solution such as glucose or amino acid, or, if needed, can be administered alone intramuscularly, intracutaneously, subcutaneously, or intraperitoneally. A suppository is administered per rectally. The dosage of the medicinal preparation should be selected as is appropriate to the usage, patient's age, sex, disease condition, and other conditions. It is usually 0.01-100 mg, preferably 0.1-50 mg, per day or kg body weight, administered once or divided over a number of doses.

[0150]

Of course, since the dosage varies depending on a variety of conditions, as mentioned above, there are cases in which a dosage lower than the above range is adequate and cases in which a dosage higher than the above range is necessary.

[0151]

Application Examples

The present invention is explained in detail below through reference examples, Application Examples, production examples, and test examples.

Reference Example 1

Synthesis of 4-[(5-nitro-2-pyridinyl)oxy]-1-indanone

1.0 g of 4-hydroxy-1-indanone, 1.07 g of 2-chloro-5-nitropyridine, and 5 g of anhydrous potassium carbonate were dissolved in 10 mL of N,N-dimethylformamide (DMF) and stirred for 17 h at room temperature. After the reaction had been completed, 50 mL of water were added to the reaction solution, and extraction was performed with ethyl acetate. The organic (ethyl acetate) layer was washed with water and dried on anhydrous sodium sulfate. The solvent was distilled off. The residue obtained was recrystallized using ethyl acetate to obtain the title compound (1.36 g, light yellow powder).

Melting point: 130-132°C

Reference Example 2

Production of 4-[(5-amino-2-pyridinyl)oxy]-1-indanone

1.0 g of the 4-[(5-nitro-2-pyridinyl)oxy]-1-indanone obtained in Reference Example 1 was dissolved in 25 mL of methanol and catalytically reduced at normal pressure at room temperature in the presence of 100 mg of 10% palladium-carbon. After 20 h, the catalyst was filtered out. The filtrate was concentrated under reduced pressure to obtain a brown solid. 840 mg of the title compound in the form of a very light yellow powder were obtained by refining by silica gel column chromatography (eluent: ethyl acetate).

Melting point: 119-123°C

Reference Example 3

Production of [(5-nitropyrimidin-2-yl)oxy]indanon-1-one

1.98 g of 4-hydroxy-1-indanone, 2.13 g of 2-chloro-5-nitropyrimidine produced according to the method described in the literature (A. Signor, E. Scoffone, L. Biondi, S. Bezzi, Gazz. Chim. Ital., 93, 65, 1963), and 0.92 g of anhydrous potassium carbonate were stirred in 20 mL of dimethylformamide for 2 h at room temperature. 200 mL of water were poured into the reaction solution, and extraction was performed with 200 mL of ethyl acetate. The organic layer was washed with a saturated sodium bicarbonate aqueous solution followed by saturated saline, then dried on anhydrous sodium sulfate. The solvent was distilled off under reduced pressure.

The solid residue was refined by silica gel column chromatography (eluent: n hexane: ethyl acetate = 2:1) to obtain 0.61 g of the title compound. Yellow, crystalline powder.

[0152]

^{1}H-NMR ($CDCl_3$) δ ppm: 2.70-2.75 (m, 2H), 2.97-3.01 (m, 2H), 7.41-7.44 (m, 1H), 7.49-7.55 (m, 1H), 7.76-7.79 (m, 1H), 9.35 (s, 2H).

Reference Example 4

Production of 4-[(5-aminopyrimidin-2-yl)oxy]indanon-1-one

0.45 g of the 4-[(5-nitropyrimidin-2-yl)oxy]indanon-1-one produced in Reference Example 3 was dissolved in a mixture of 10 mL of ethyl acetate and 5 mL of acetic acid. 0.1 g of 5% palladium-carbon was added and stirred for 4 h at room temperature under hydrogen partial pressure. The filtrate was filtered using Celite, and the filtrate was concentrated under reduced pressure. The oily residue was dissolved in ethyl acetate, washed with a saturated sodium bicarbonate aqueous solution followed by saturated saline, and then dried on anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. After vacuum drying, 0.37 g of the title compound was obtained. Brownish-yellow, amorphous powder.

[0153]

^{1}H-NMR ($CDCl_3$) δ ppm: 2.66-2.70 (m, 2H), 2.96-3.01 (m, 2H), 7.35-7.48 (m, 2H), 7.65 (dd, 1H), 8.07 (s, 2H).

Reference Example 5

Production of 5-(4-nitrophenoxy)-3,4-dihydronaphthalen-1(2H)-one

3.77 g of 4-chloronitrobenzene, 3.23 g of 5-hydroxy-1-tetralone, and 1.65 g of anhydrous potassium carbonate were stirred in 30 mL of dimethylformamide for 48 h at 80°C. 300 mL of water were poured into the reaction solution, and extraction was performed with 300 mL of ethyl acetate. The organic layer was washed with saturated saline and dried on anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The solid residue was refined by silica gel column chromatography (eluent: n-hexane: ethyl acetate = 3:1) to obtain 2.67 g of the title compound. Yellow, crystalline powder.

[0154]

^{1}H-NMR ($CDCl_3$) δppm: 2.07-2.16 (m, 2H), 2.68 (t, 2H), 2.82 (t, 2H), 6.96 (d, 2H), 7.23-7.26 (m, 1H), 7.37-7.43 (m, 1H), 8.00 (dd, 1H), 8.22 (d, 2H).

Reference Example 6

Production of 5-(4-nitrophenoxy)-3,4-dihydronaphthalen-1-yl acetate

1.05 g of the 5-(4-nitrophenoxy)-3,4-dihydronaphthalen-1(2H)-one produced in Reference Example 5, 6.12 mL of isopropenyl acetate, and 35 mg of p-toluenesulfonic acid monohydrate were stirred at 80-120°C. After 48 h, the reaction solution was concentrated under reduced pressure. The oily residue was dissolved in ethyl acetate, washed sequentially with a saturated sodium bicarbonate aqueous solution and saturated saline, and then dried on anhydrous sodium sulfate. The solvent was distilled off under reduced pressure to obtain 1.24 g of the target compound. Very light yellow powder.

[0155]

^{1}H-NMR ($CDCl_3$) δppm: 2.33 (s, 3H), 2.37-2.45 (m, 2H), 2.74 (t, 2H), 5.77 (t, 1H), 6.93-6.96 (m, 3H), 7.03-7.06 (m, 1H), 7.22-7.27 (m, 1H), 8.20

Reference Example 7

Production of 5-(4-aminophenoxy)-3,4-dihydronaphthalen-1-yl acetate

0.37 g of the 5-(4-nitrophenoxy)-3,4-dihydronaphthalen-1-yl acetate produced in Reference Example 6 was suspended in 10 mL of acetic acid, and 0.37 g of zinc powder and 1.42 mL of 4N HCl/dioxane were added. After stirring for 40 min at room temperature, the reaction solution was filtered, and the filtrate was concentrated under reduced pressure. The oily residue was dissolved in ethyl acetate, washed sequentially with saturated a sodium bicarbonate aqueous solution and saturated saline, and dried on anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The oily residue was refined by silica gel column chromatography

(eluent: n-hexane: ethyl acetate = 2:1) to obtain 0.18 g of the title compound. Yellow, crystalline powder.

[0156]

^{1}H-NMR ($CDCl_3$) δ ppm: 2.30 (s, 3H), 2.40-2.48 (m, 2H), 2.91 (t, 2H), 5.73 (t, 1H), 6.64-6.85 (m, 6H), 7.04-7.10 (m, 1H).

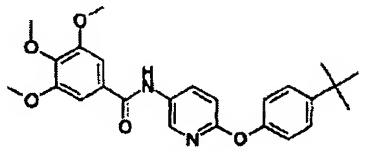
Compounds with the chemical structures shown in Tables 1-58 below (Application Examples 1-220) were synthesized.

[0157]

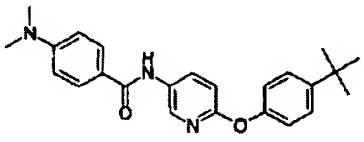
Table 1

[Tables 1-58: Key: 1 Application Example __]

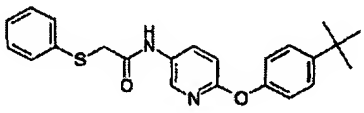
① 实施例 1



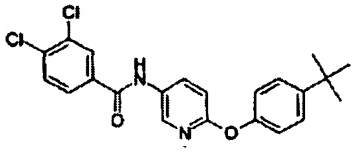
① 实施例 2



① 实施例 3

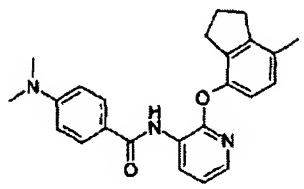
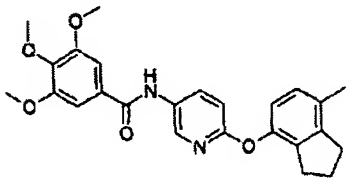
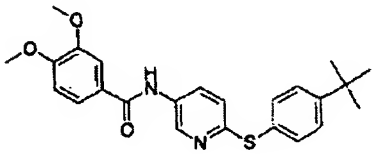
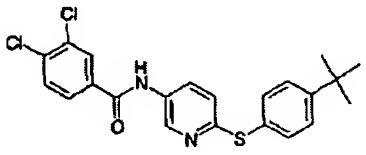


① 实施例 4



[0158]

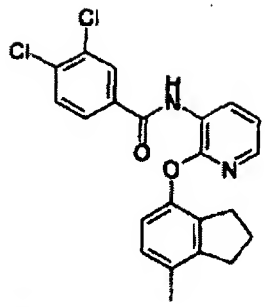
Table 2

① 実施例 5	
① 実施例 6	
① 実施例 7	
① 実施例 8	

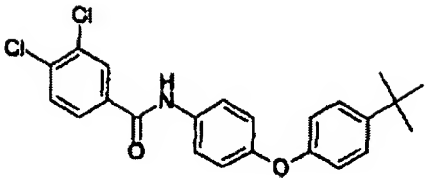
[0159]

Table 3

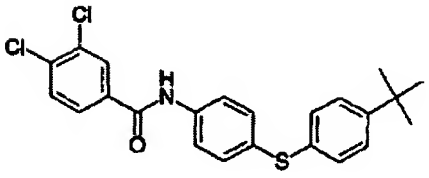
① 実施例９



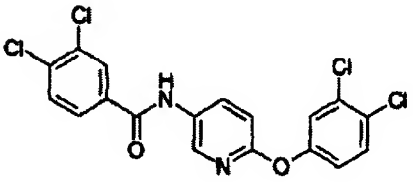
① 実施例１０



① 実施例１１



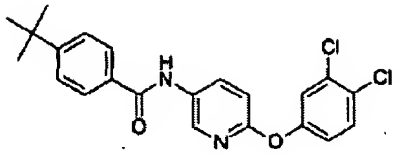
① 実施例１２



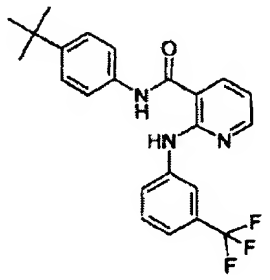
[0160]

Table 4

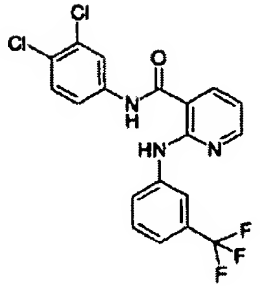
① 実施例１３



① 実施例１４



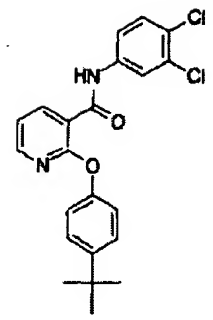
① 実施例１５



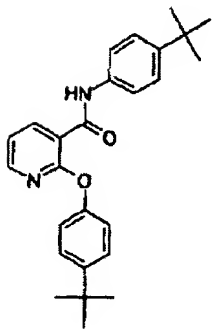
[0161]

Table 5

① 実施例１６

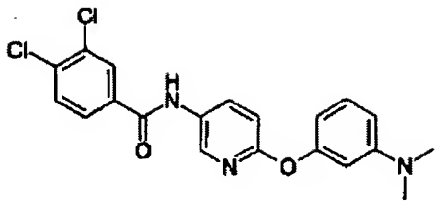
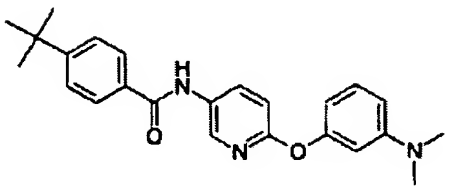
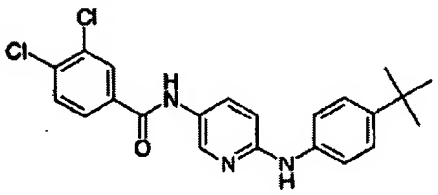
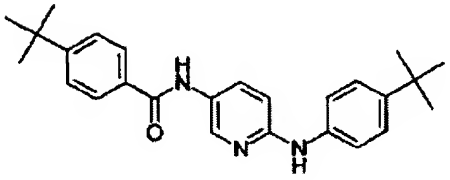


① 実施例１７



[0162]

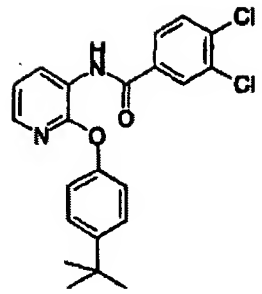
Table 6

①実施例１８	
①実施例１９	
①実施例２０	
①実施例２１	

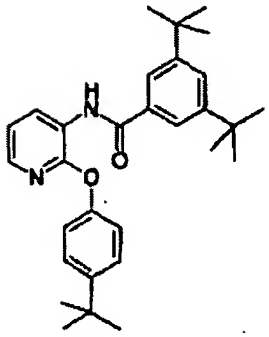
[0163]

Table 7

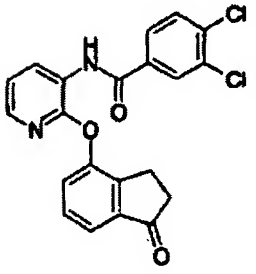
① 実施例２２



① 実施例２３



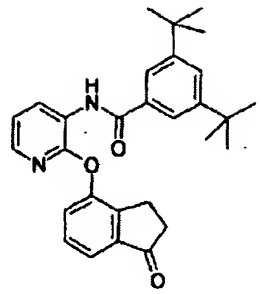
① 実施例２４



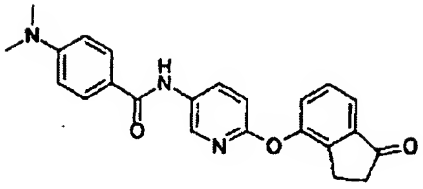
[0164]

Table 8

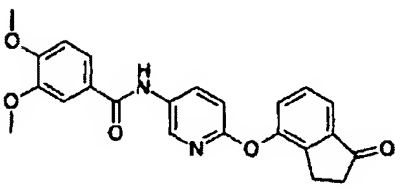
① 実施例２５



① 実施例２６

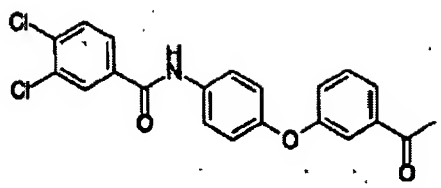
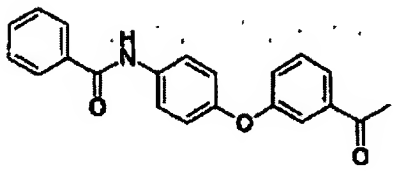
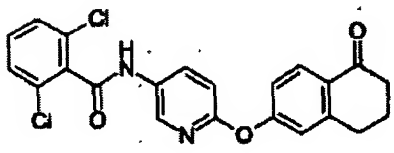
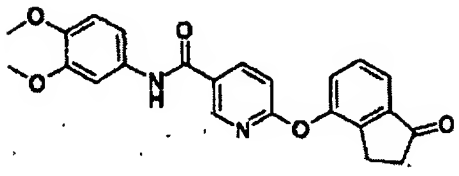


① 実施例２７



[0165]

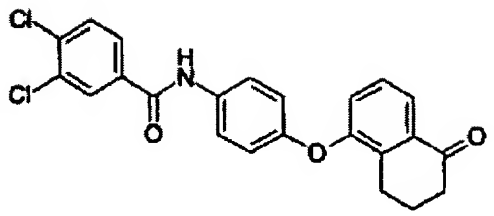
Table 9

① 実施例２８	
① 実施例２９	
① 実施例３０	
① 実施例３１	

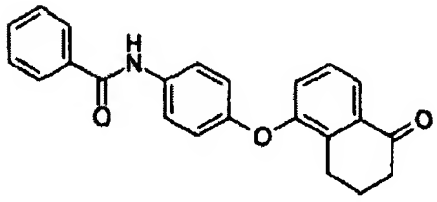
[0166]

Table 10

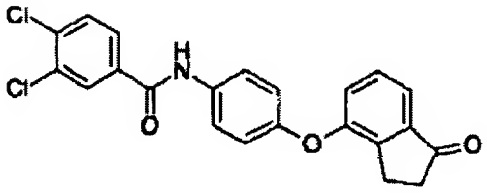
① 実施例３２



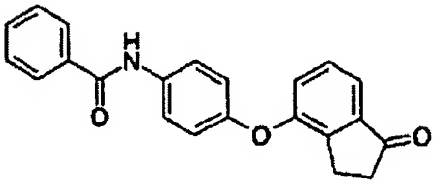
① 実施例３３



① 実施例３４

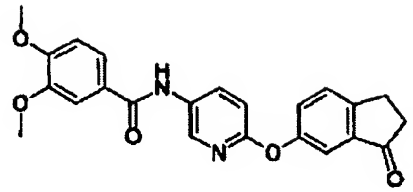
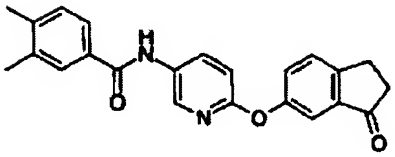
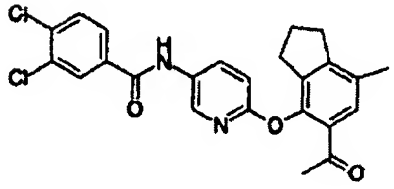
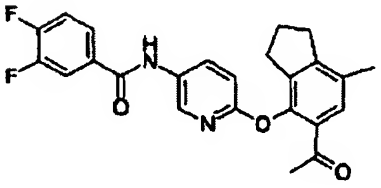


① 実施例３５



[0167]

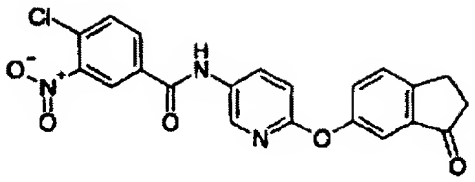
Table 11

① 実施例３６	
① 実施例３７	
① 実施例３８	
① 実施例３９	

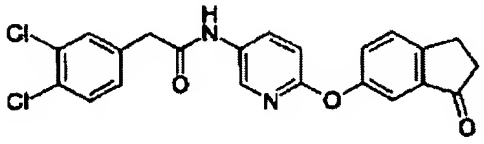
[0168]

Table 12

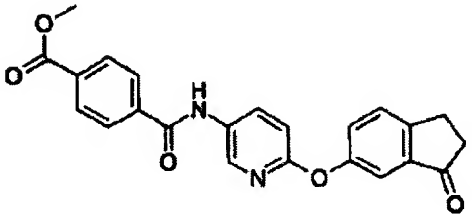
① 実施例４０



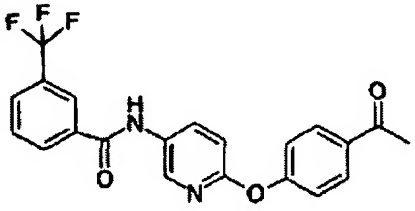
① 実施例４１



① 実施例４２

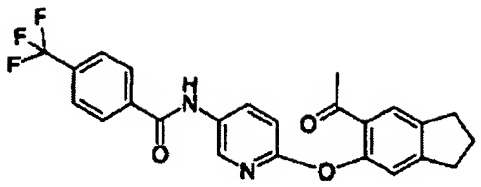
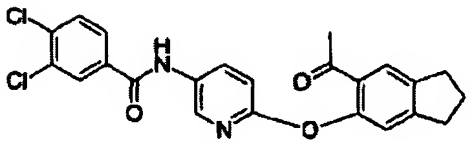
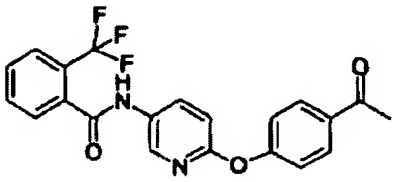
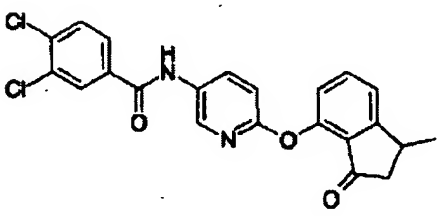


① 実施例４３



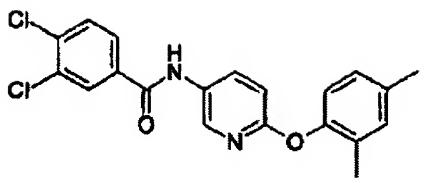
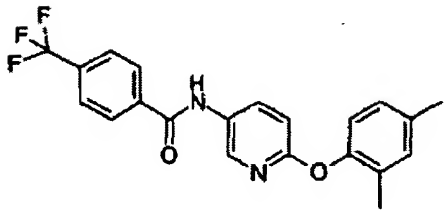
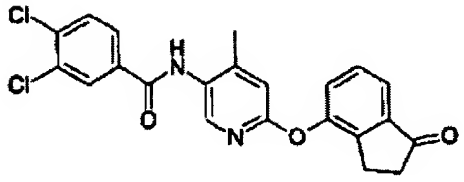
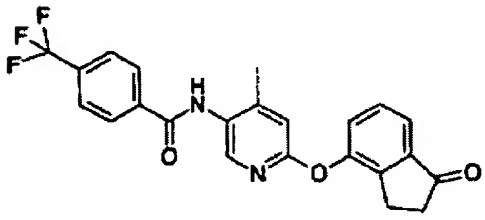
[0169]

Table 13

①実施例４４	
①実施例４５	
①実施例４６	
①実施例４７	

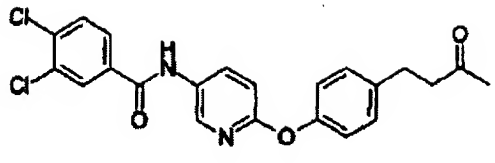
[0170]

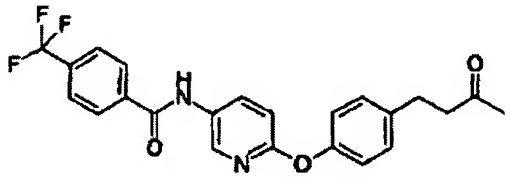
Table 14

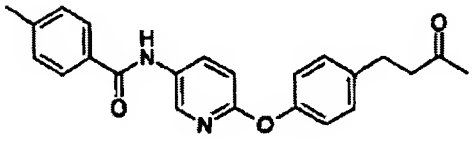
①実施例４８	
①実施例４９	
①実施例５０	
①実施例５１	

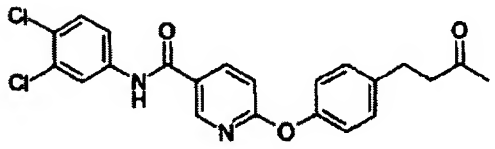
[0171]

Table 15

実施例５２ 

実施例５３ 

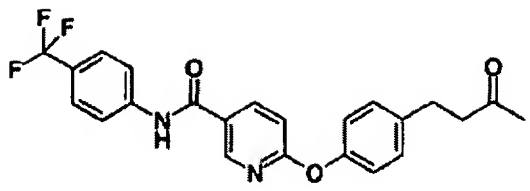
実施例５４ 

実施例５５ 

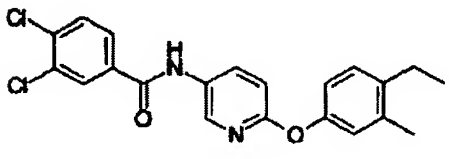
[0172]

Table 16

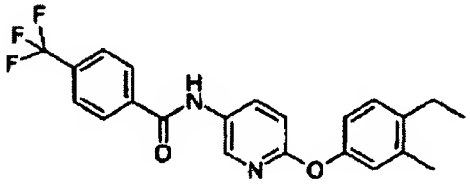
① 実施例５６



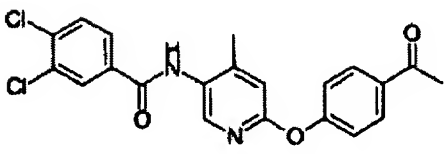
① 実施例５７



① 実施例５８



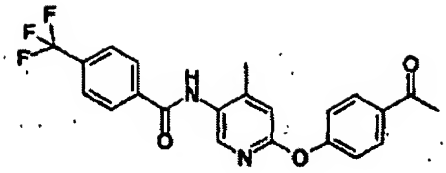
① 実施例５９



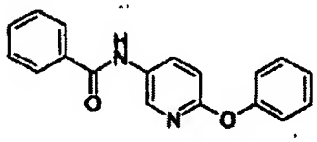
[0173]

Table 17

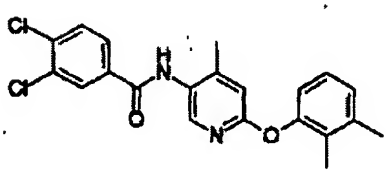
① 実施例６０



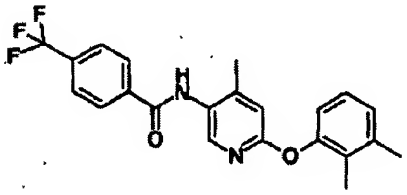
① 実施例６１



① 実施例６２



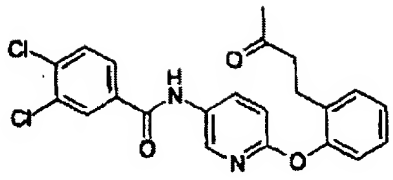
① 実施例６３



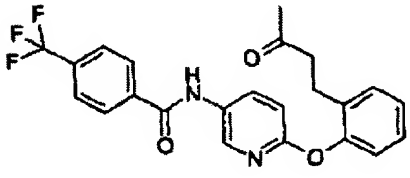
[0174]

Table 18

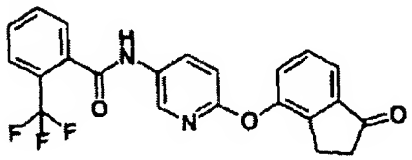
① 実施例６４



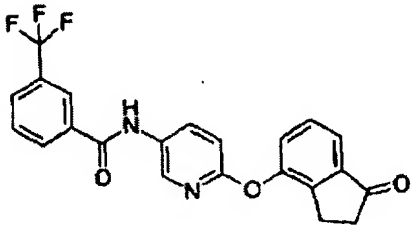
① 実施例６５



① 実施例６６

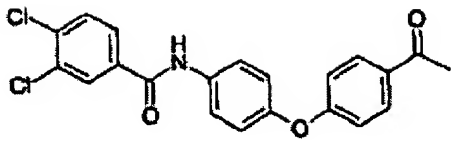
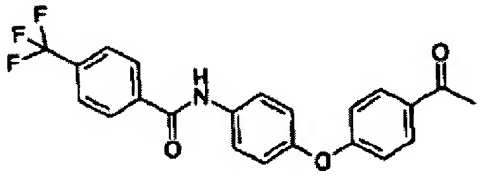
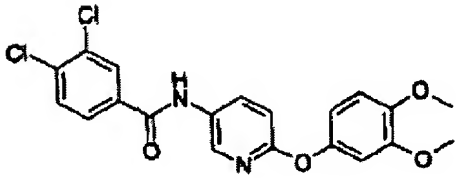


① 実施例６７



[0175]

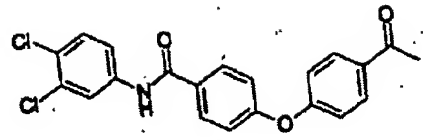
Table 19

①	実施例６８	
①	実施例６９	
①	実施例７０	

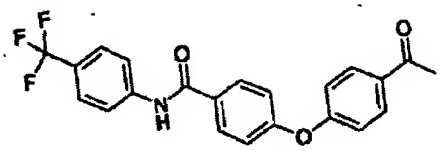
[0176]

Table 20

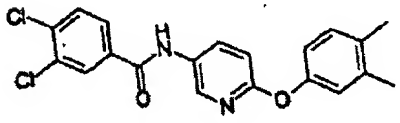
① 実施例７１



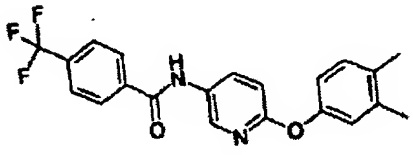
① 実施例７２



① 実施例７３

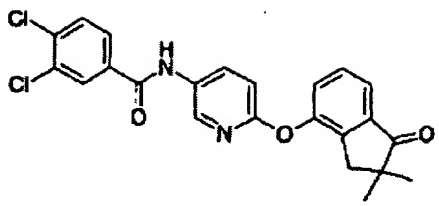
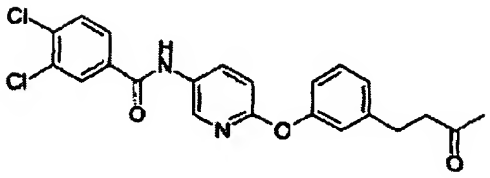
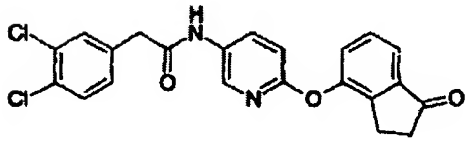
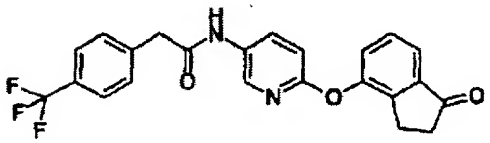


① 実施例７４



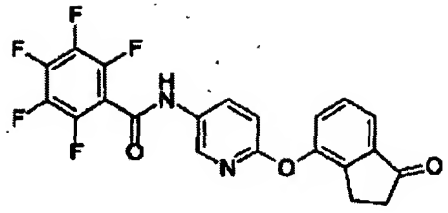
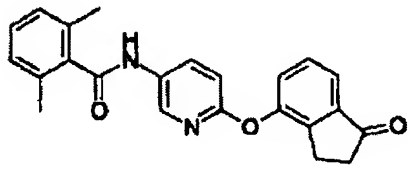
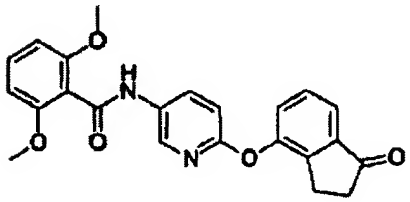
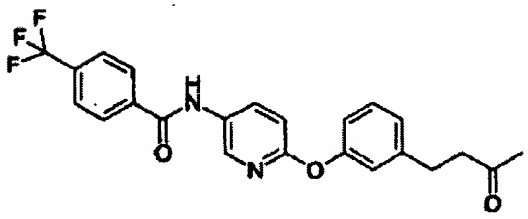
[0177]

Table 21

①実施例７５	
①実施例７６	
①実施例７７	
①実施例７８	

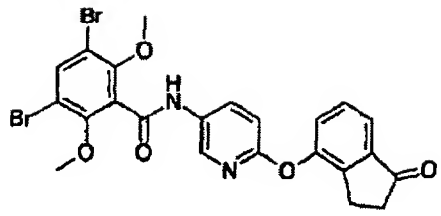
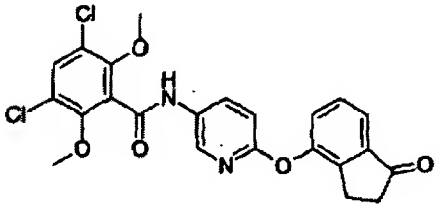
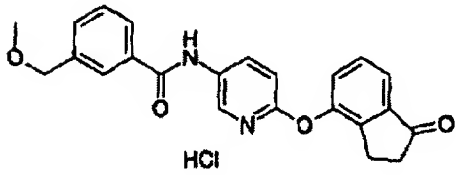
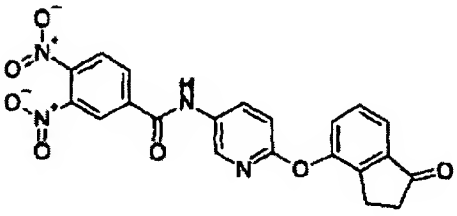
[0178]

Table 22

① 実施例79	
① 実施例80	
① 実施例81	
① 実施例82	

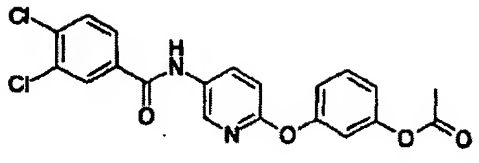
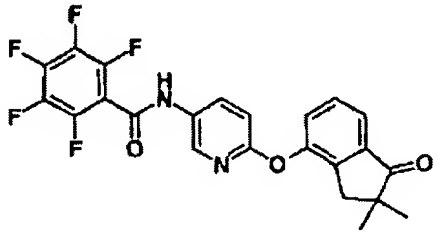
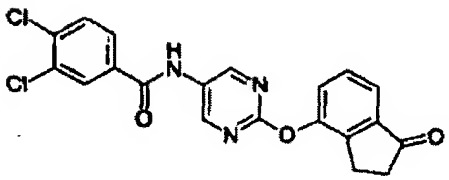
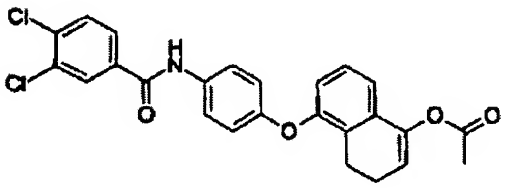
[0179]

Table 23

①実施例８３	
①実施例８４	
①実施例８５	
①実施例８６	

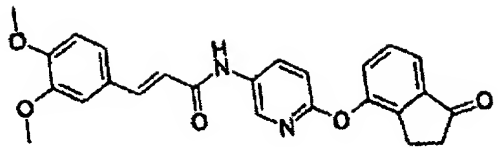
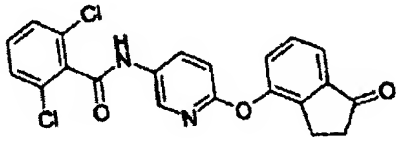
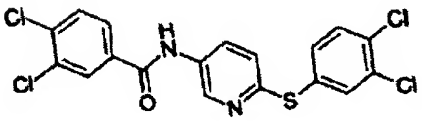
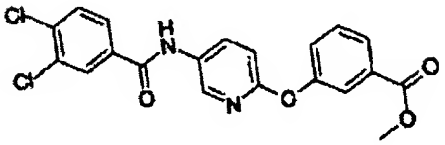
[0180]

Table 24

①実施例87	
①実施例88	
①実施例89	
①実施例90	

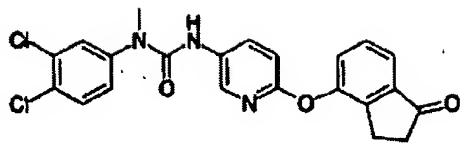
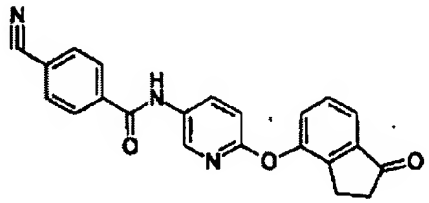
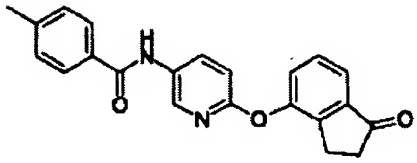
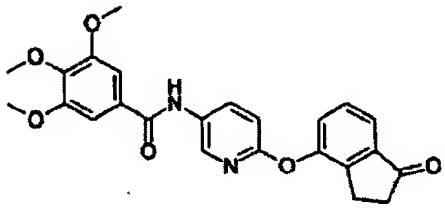
[0181]

Table 25

① 実施例９１	
① 実施例９２	
① 実施例９３	
① 実施例９４	

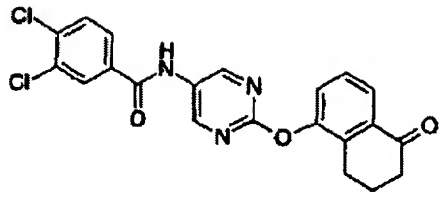
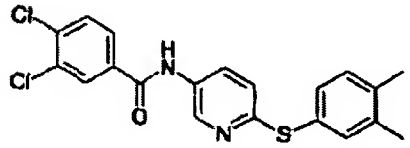
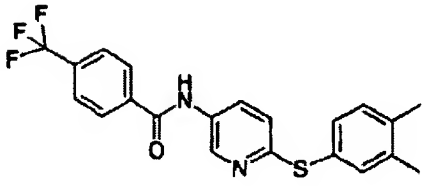
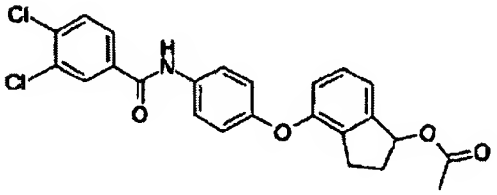
[0182]

Table 26

① 实施例95	
① 实施例96	
① 实施例97	
① 实施例98	

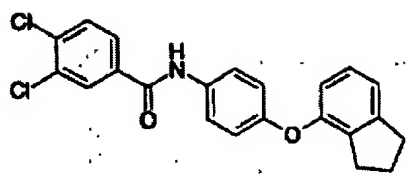
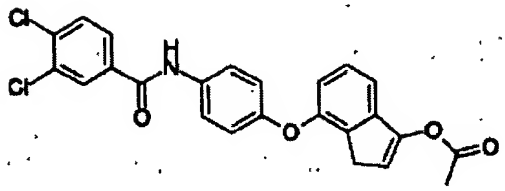
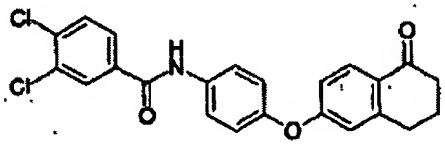
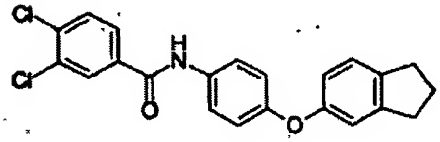
[0183]

Table 27

① 実施例９９	
① 実施例１００	
① 実施例１０１	
① 実施例１０２	

[0184]

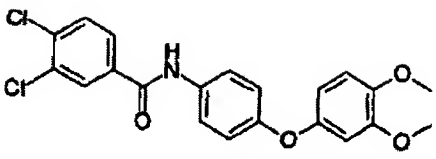
Table 28

① 実施例103	
① 実施例104	
① 実施例105	
① 実施例106	

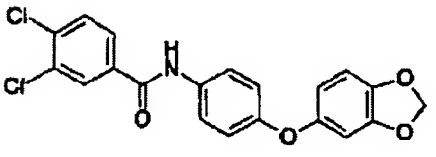
[0185]

Table 29

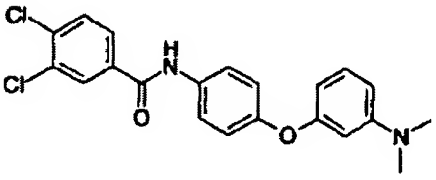
① 実施例１０７



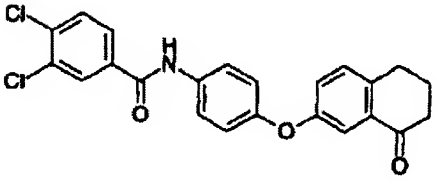
①実施例１０８



①実施例１０９



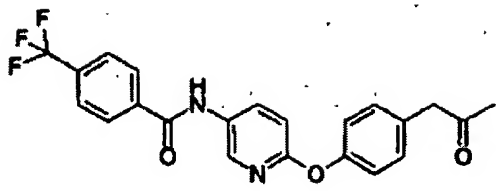
①実施例１１０



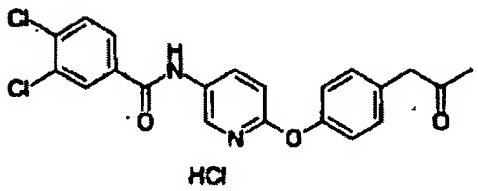
[0186]

Table 30

① 実施例１１１

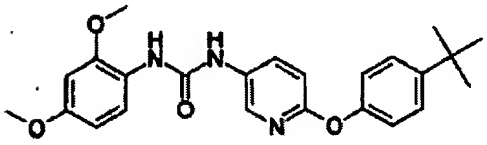


① 実施例１１２

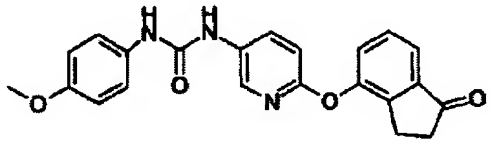


HCl

① 実施例１１３



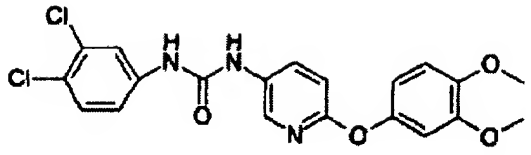
① 実施例１１４



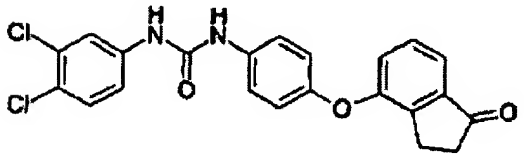
[0187]

Table 31

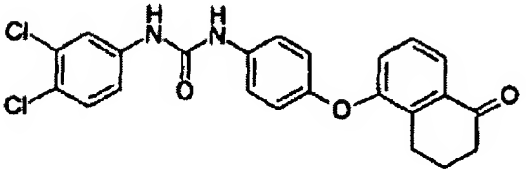
① 実施例１１５



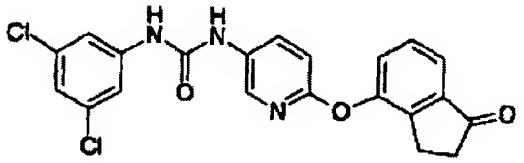
① 実施例１１６



① 実施例１１７

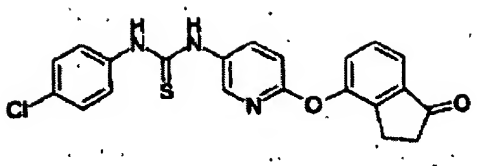
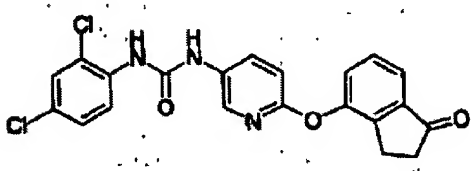
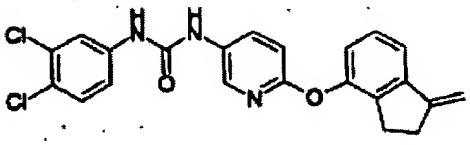
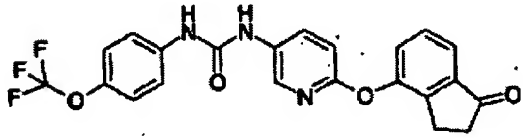


① 実施例１１８



[0188]

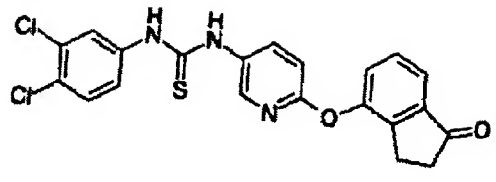
Table 32

① 実施例１１９	
① 実施例１２０	
① 実施例１２１	
① 実施例１２２	

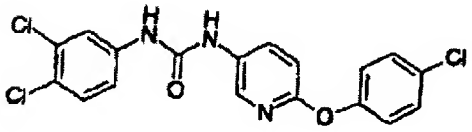
[0189]

Table 33

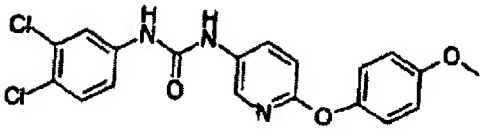
① 実施例１２３



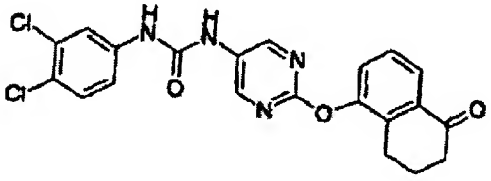
① 実施例１２４



① 実施例１２５

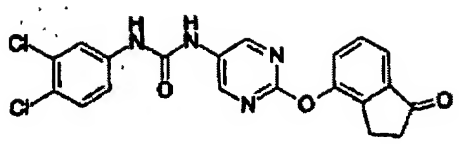
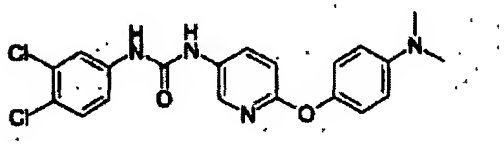
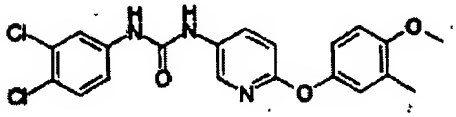
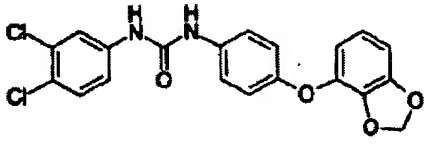


① 実施例１２６



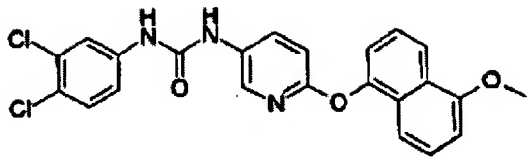
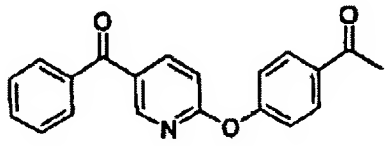
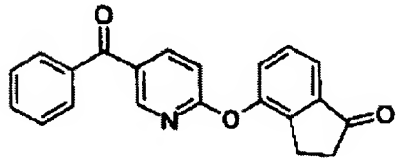
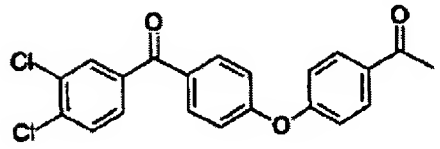
[0190]

Table 34

① 実施例１２７	
① 実施例１２８	
① 実施例１２９	
① 実施例１３０	

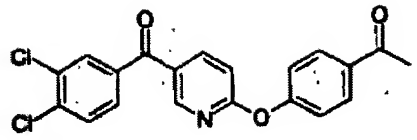
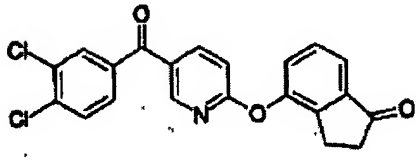
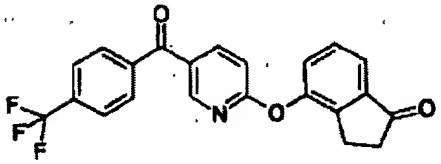
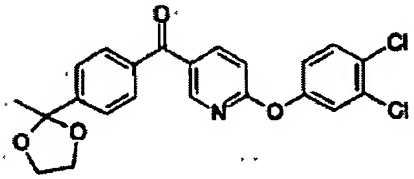
[0191]

Table 35

①実施例１３１	
①実施例１３２	
①実施例１３３	
①実施例１３４	

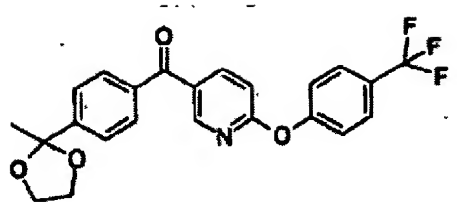
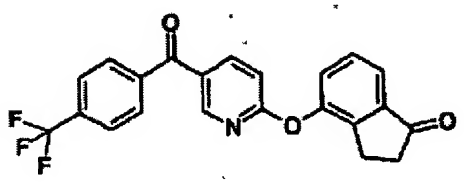
[0192]

Table 36

実施例135	
実施例136	
実施例137	
実施例138	

[0193]

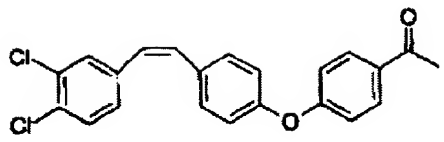
Table 37

①	実施例１３９	
①	実施例１４０	

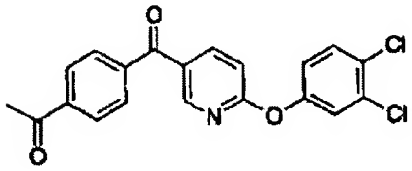
[0194]

Table 38

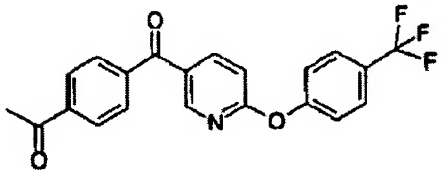
① 実施例１４１



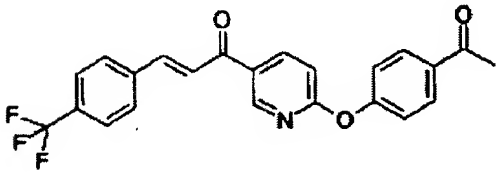
① 実施例１４２



① 実施例１４３

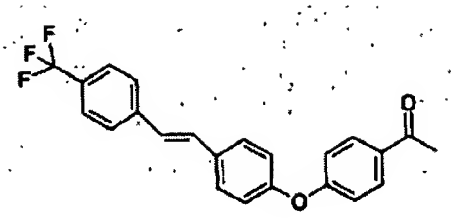
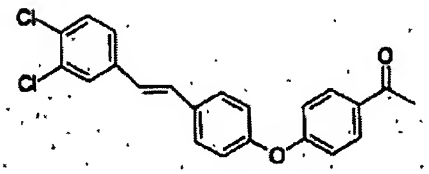
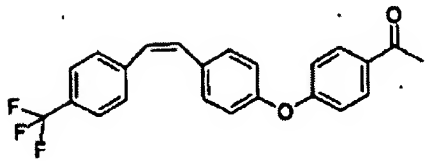
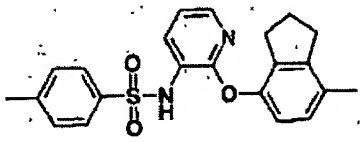


① 実施例１４４



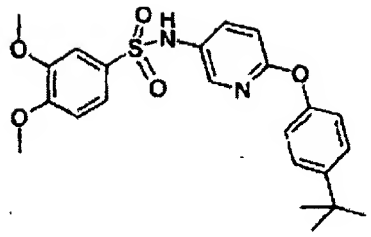
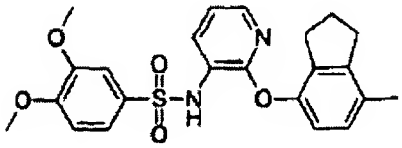
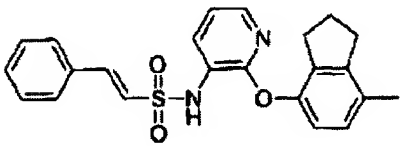
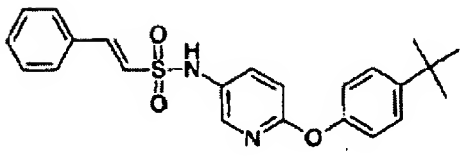
[0195]

Table 39

①実施例１４５	
①実施例１４６	
①実施例１４７	
①実施例１４８	

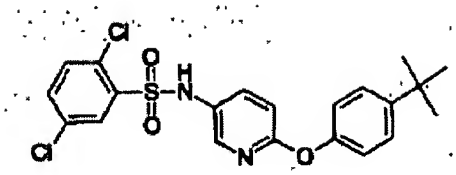
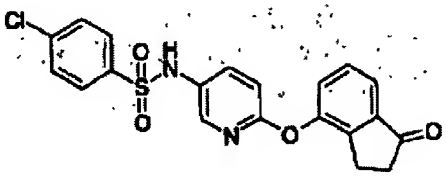
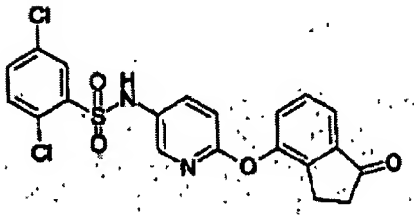
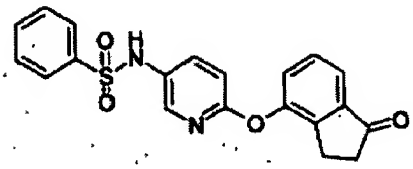
[0196]

Table 40

①実施例１４９	
①実施例１５０	
①実施例１５１	
①実施例１５２	

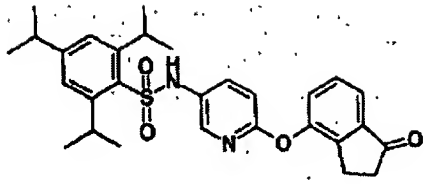
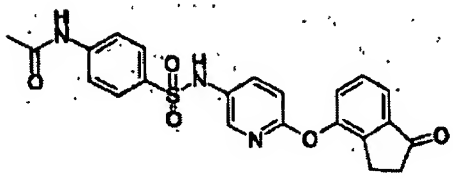
[0197]

Table 41

① 実施例１５３	
① 実施例１５４	
① 実施例１５５	
① 実施例１５６	

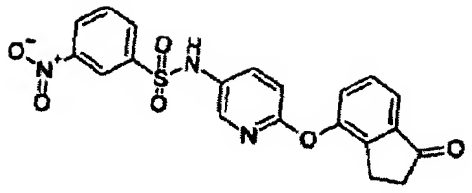
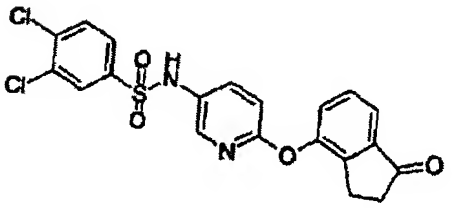
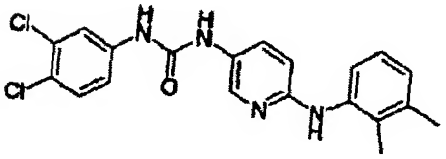
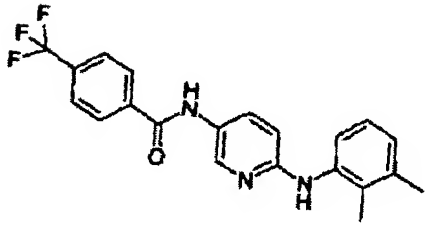
[0198]

Table 42

① 実施例１５７	
① 実施例１５８	

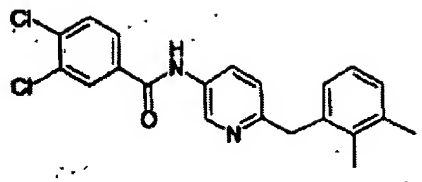
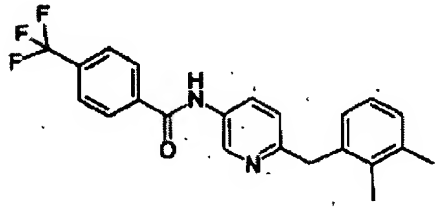
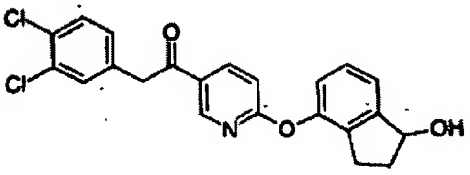
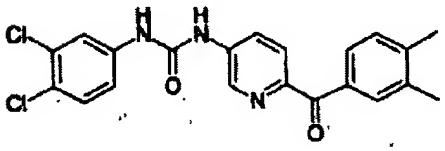
[0199]

Table 43

①実施例159	
①実施例160	
①実施例161	
①実施例162	

[0200]

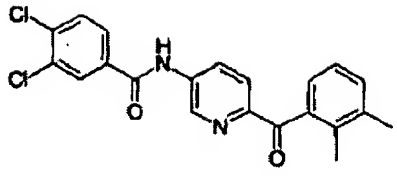
Table 44

① 実施例１６３	
① 実施例１６４	
① 実施例１６５	
① 実施例１６６	

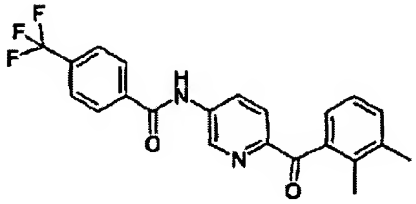
[0201]

Table 45

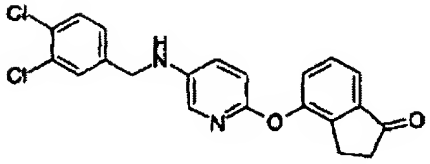
① 実施例１６７



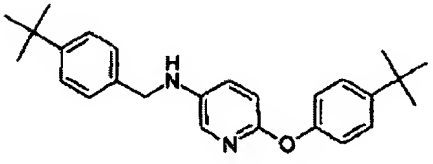
① 実施例１６８



① 実施例１６９

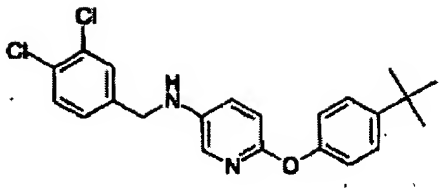
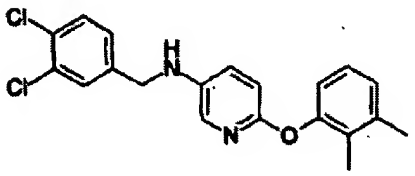
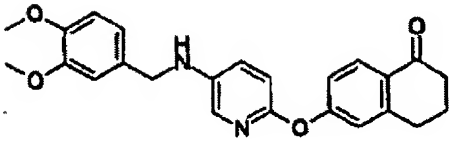
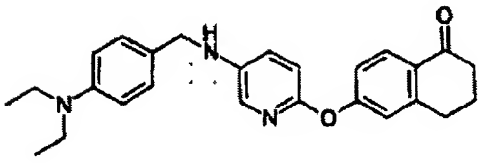


① 実施例１７０



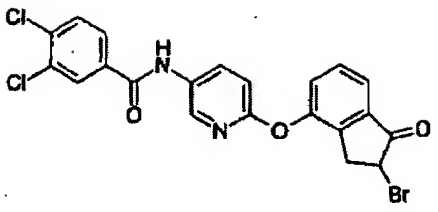
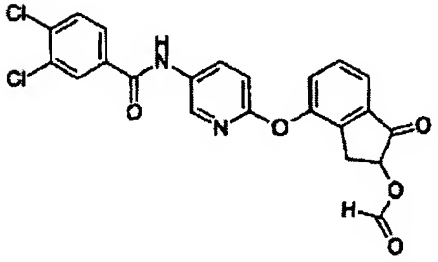
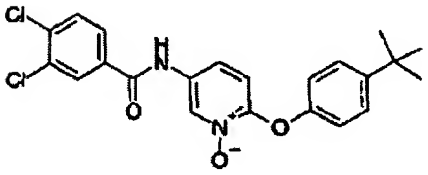
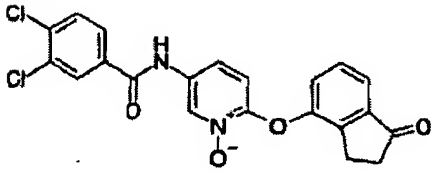
[0202]

Table 46

①実施例１７１	
①実施例１７２	
①実施例１７３	
①実施例１７４	

[0203]

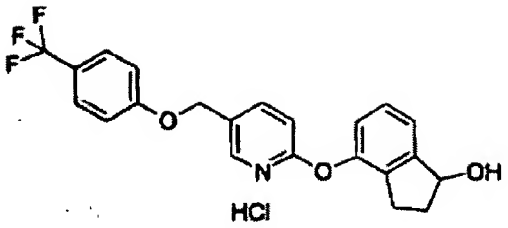
Table 47

①実施例１７５	
①実施例１７６	
①実施例１７７	
①実施例１７８	

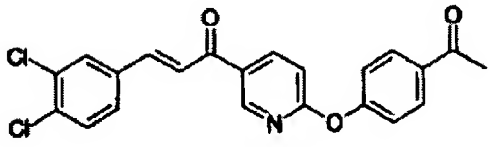
[0204]

Table 48

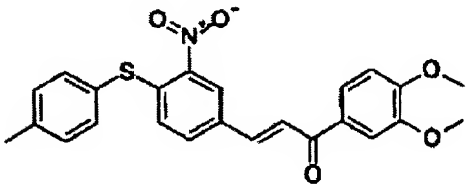
①実施例１７９



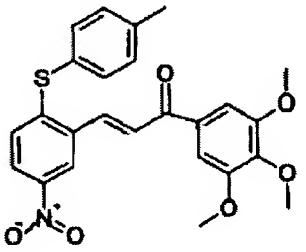
①実施例１８０



①実施例１８１

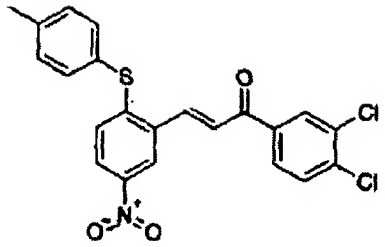
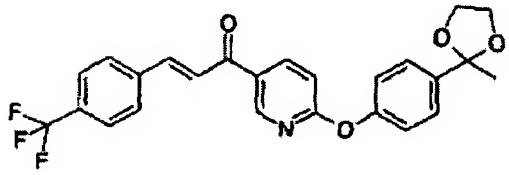
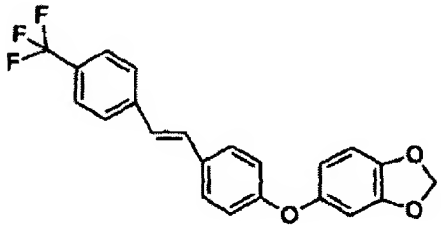
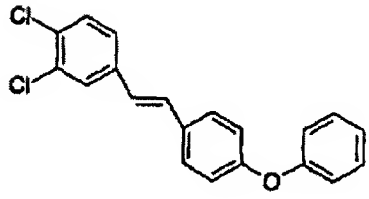


①実施例１８２



[0205]

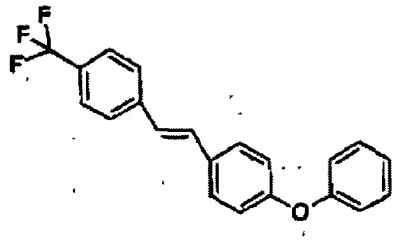
Table 49

実施例１８３	
実施例１８４	
実施例１８５	
実施例１８６	

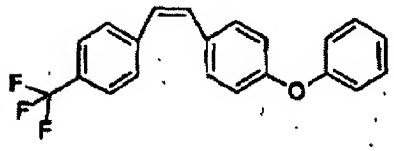
[0206]

Table 50

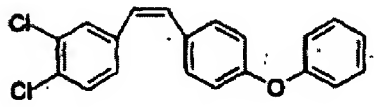
① 実施例１８７



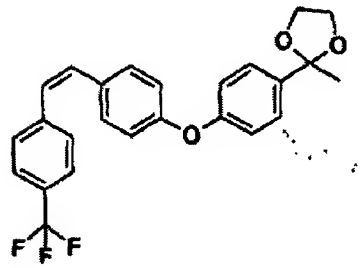
① 実施例１８８



① 実施例１８９

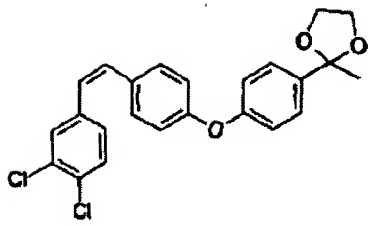
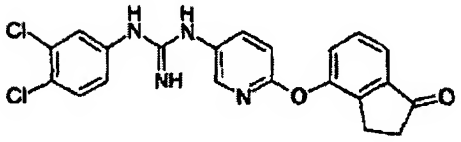
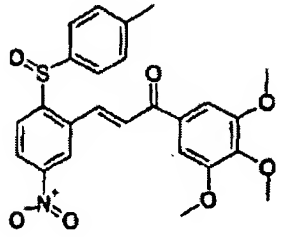
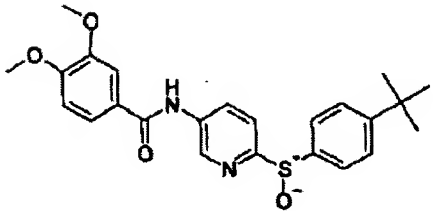


① 実施例１９０



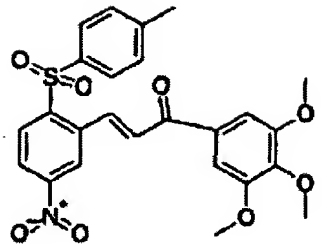
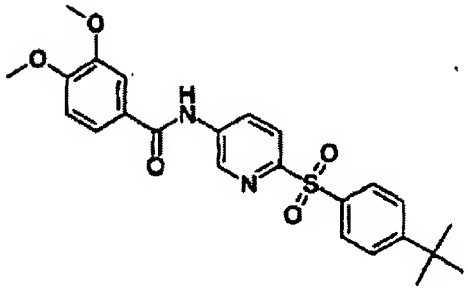
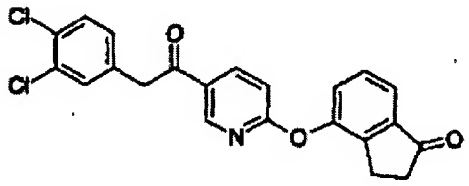
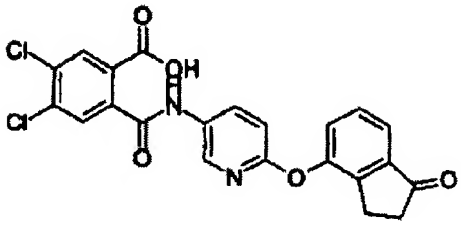
[0207]

Table 51

① 実施例１９１	
① 実施例１９２	
① 実施例１９３	
① 実施例１９４	

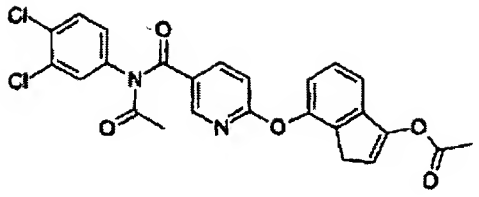
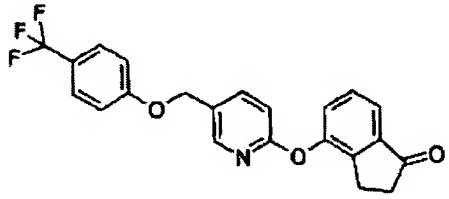
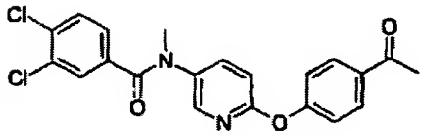
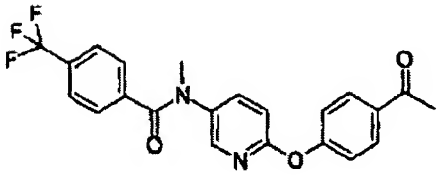
[0208]

Table 52

① 実施例１９５	
① 実施例１９６	
① 実施例１９７	
① 実施例１９８	

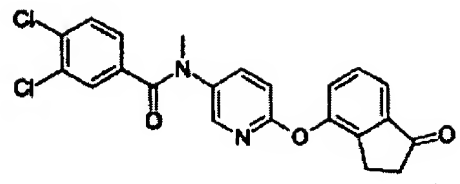
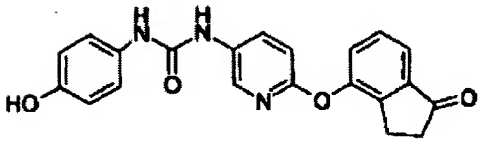
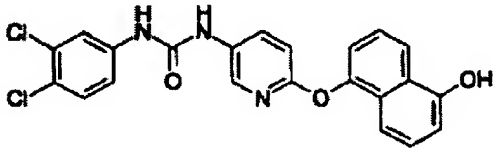
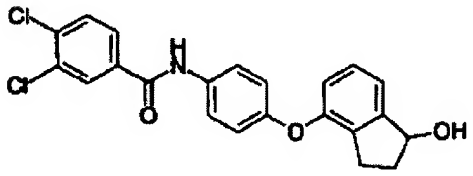
[0209]

Table 53

実施例１９９	
実施例２００	
実施例２０１	
実施例２０２	

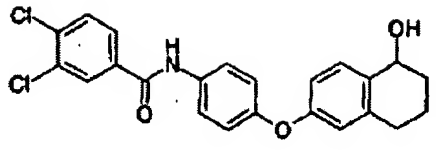
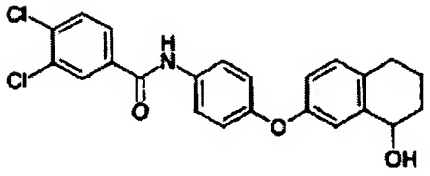
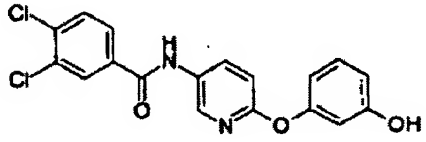
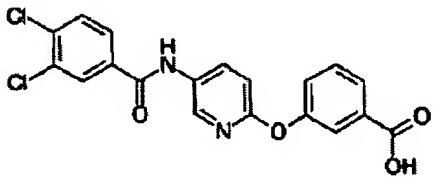
[0210]

Table 54

① 実施例２０３	
① 実施例２０４	
① 実施例２０５	
① 実施例２０６	

[0211]

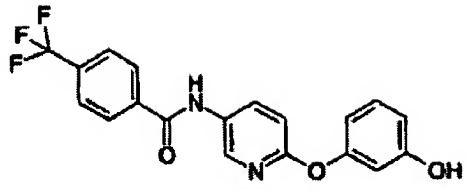
Table 55

①実施例２０７	
実施例２０８	
①実施例２０９	
①実施例２１０	

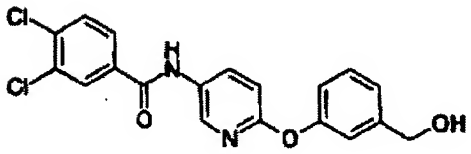
[0212]

Table 56

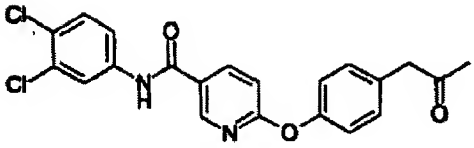
① 実施例２１１



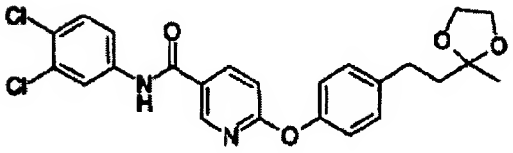
① 実施例２１２



① 実施例２１３



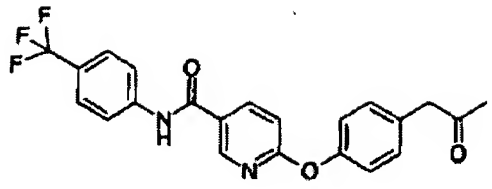
① 実施例２１４



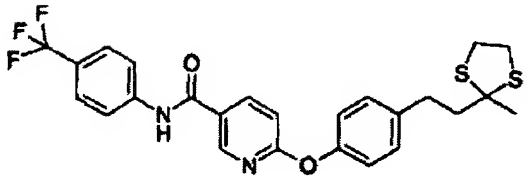
[0213]

Table 57

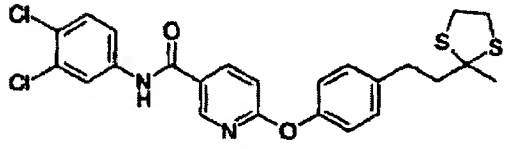
① 実施例２１５



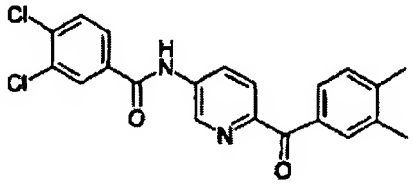
① 実施例２１６



① 実施例２１７



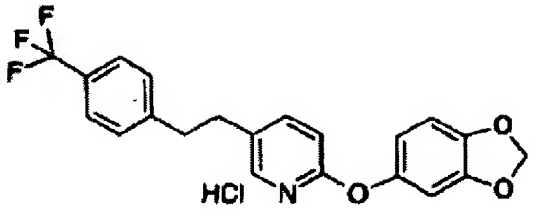
① 実施例２１８



[0214]

Table 58

① 実施例219



[0215]

The methods of producing the above compounds and their NMR or mass spectrum data appear below.

Application Example 1

Production of N-{6-[4-(tert-butyl)phenoxy]pyridin-3-yl}-3,4,5-trimethoxybenzamide

3-Amino-6-[4-(tert-butyl)phenoxy]pyridine (500 mg), 430 mg of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, and 290 mg of 1-hydroxybenzotriazole monohydrate were added to 5 mL of an N,N-dimethylformamide solution of 440 mg of 3,4,5-trimethoxybenzoic acid while cooling. The reaction solution was stirred for one day while returning to room temperature. Ethyl acetate and water were added to the reaction solution. The organic layer was separated, washed with a saturated sodium bicarbonate aqueous solution and water, and dried by anhydrous magnesium sulfate. The solvent was distilled off. The residue was refined by silica gel column to obtain 750 mg of the title compound.

^{1}H-NMR ($CDCl_3$) δppm: 1.32 (s, 9H), 3.89(s, 9H), 6.91 (d, 1H, J=8.9 Hz), 7.02-7.07 (m, 4H), 7.37-7.41 (m, 2H), 7.99 (brs, 1H), 8.17 (dd, 1H, J=2.6 Hz, 8.9 Hz), 8.25 (d, 1H, J=2.6Hz).

[0216]

The compounds of Application Examples 2-87 below were produced by the same method.

Application Example 2

^{1}H-NMR ($CDCl_3$) δppm: 1.33 (s, 9H), 3.

04 (s, 6H), 6.69 (d, 2H, J = 8.9 Hz), 6.88-6.91 (m, 1H), 7.03-7.06 (m, 2H), 7.34-7.40 (m, 2H), 7.76-7.79 (m, 3H), 8.21-8.25 (m, 2H).

Application Example 3

^{1}H-NMR ($CDCl_3$) δ ppm : 1.32 (s, 9H), 3.77(s, 2H), 6.86 (d, 1H, J = 8.9 Hz), 7.00-7.03 (m, 2H), 7.24-7.40 (m, 7H), 7.99 (dd, 1H, J = 3.0 Hz, 8.9 Hz), 8.08 (d, 1H, J = 3.0 Hz), 8.53 (brs, 1H).

Application Example 4

^{1}H-NMR ($CDCl_3$) δ ppm : 1.28 (s, 9H), 6.83 (d, 1H, J = 8.9 Hz), 6.92-6.97 (m, 2H), 7.29-7.34 (m, 2H), 7.43 (d, 1H, J = 8.2 Hz), 7.61-7.65 (m, 1H), 7.90 (d, 1H, J = 2.3 Hz), 8.06-8.10 (m, 1H), 8.17 (d, 1H, J = 2.6 Hz), 8.82 (brs, 1H).

Application Example 5

^{1}H-NMR ($CDCl_3$) δ ppm : 1.92-2.00 (m, 2H), 2.20 (s, 3H), 2.53-2.59 (m, 2H), 2.75-2.81 (m, 2H), 2.91 (s, 6H), 6.64 (d, 2H, J = 8.9 Hz), 6.78 (d, 1H, J = 8.2 Hz), 6.87-6.96 (m, 2H), 7.10 (d, 2H, J = 8.9 Hz), 7.51 (brs, 1H), 7.67-7.70 (m, 1H), 8.56 (dd, 1H, J = 1.6 Hz, 7.9 Hz).

Application Example 6

^{1}H-NMR ($CDCl_3$) δ ppm : 1.98-2.09 (m, 2H), 2.25 (s, 3H), 2.70-2.75 (m, 2H), 2.86 (t, 2H, J = 7.6 Hz), 3.89 (s, 9H), 6.65 (d, 1H, J = 8.2 Hz), 6.88 (d, 1H, J = 8.9 Hz), 6.99 (d, 1H, J = 7.9 Hz), 7.07 (s, 2H), 7.94 (brs, 1H), 8.13-8.17 (m, 1H), 8.21 (d, 1H, J = 2.6 Hz).

Application Example 7

^{1}H-NMR ($CDCl_3$) δ ppm : 1.34 (s, 9H), 3.93 (s, 3H), 3.94 (s, 3H), 6.89 (d, 1H, J = 8.2 Hz), 6.96 (d, 1H, J = 8.9 Hz), 7.38-7.52 (m, 6H), 7.93 (brs, 1H), 8.07 (dd, 1H, J = 2.6 Hz, 8.6 Hz), 8.49 (d, 1H, J =2.6 Hz).

Application Example 8

^{1}H−NMR ($CDCl_3$) δ ppm : 1.34 (s, 9H), 6.95 (d, 1H), 7.42-7.52(m, 4H), 7.56 (d, 1H), 7.67-7.71- (m, 1H), 7.90 (brs, 1H), 7.96 (d, 1H), 8.01-8.05 (m, 1H), 8.48 (d, 1H).

Application Example 9

^{1}H−NMR ($CDCl_3$) δ ppm : 2.01-2.12 (m, 2H), 2.27 (s, 3H), 2.72(t, 2H, J = 7.6 Hz), 2.86-2.91 (m, 2H), 6.90 (d, 1H, J = 7.9 Hz), 7.00-7.06 (m, 2H), 7.57 (d, 1H, J = 8.2 Hz), 7.70-7.73 (m, 1H), 7.85-7.87 (m, 1H), 8.01 (d, 1H, J = 1.9 Hz), 8.52 (brs, 1H), 8.80-8.83 (m, 1H).

Application Example 10

^{1}H−NMR ($CDCl_3$) δ ppm : 1.33 (s, 9H), 6.91-6.97 (m, 2H), 6.99-7.05 (m, 2H), 7.32-7.38 (m, 2H), 7.57-7.67 (m, 3H), 7.69 (dd, 1H, J = 2.0 Hz, 8.2 Hz), 7.78 (brs, 1H), 7.96 (d, 1H, J = 2.0 Hz).

Application Example 11

^{1}H−NMR ($CDCl_3$) δ ppm : 1.31 (s, 9H), 7.25-7.35 (m, 6H), 7.52-7.56 (m, 3H), 7.64-7.68 (m, 1H), 7.88 (brs, 1H), 7.92-7.93 (m, 1H).

Application Example 12

^{1}H−NMR ($CDCl_3$) δ ppm : 6.99-7.03 (m, 2H), 7.27 (d, 1H, J = 2.6 Hz), 7.45 (d, 1H, J = 8.6 Hz), 7.57 (d, 1H, J = 8.2 Hz), 7.68-7.72 (m,1H), 7.88 (brs, 1H), 7.97 (d, 1H, J = 2.0 Hz), 8.19-8.25 (m, 2H).

Application Example 13

^{1}H−NMR ($CDCl_3$) δ ppm : 1.36 (s, 9H), 6.98-7.03 (m, 2H), 7.27(d, 1H, J = 2.6 Hz), 7.44 (d, 1H, J = 8.9 Hz), 7.50-7.53 (m, 2H), 7.80-7.83 (m, 2H), 8.23-8.31 (m, 2H).

Application Example 14

^{1}H−NMR ($CDCl_3$) δ ppm : 1.33 (s, 9H), 6.82 (dd, 1H, J = 4.3 Hz, 7.6 Hz), 7.23-7.26 (m, 1H), 7.37-7.48 (m, 5H), 7.78-7.87 (m, 3H), 8.08(m, 1H), 8.40 (dd, 1H, J = 1.3 Hz, 4.6 Hz), 10.50 (br s, 1H).

Application Example 15

^{1}H−NMR ($CDCl_3$) δ ppm : 6.81-6.86 (m, 1H), 7.26-7.29 (m, 1H), 7.38-7.48 (m, 3H), 7.81-7.87 (m, 4H), 8.08 (brs, 1H), 8.41-8.44 (m, 1H), 10.40 (brs, 1H).

Application Example 16

^{1}H−NMR ($CDCl_3$) δ ppm : 1.38 (s, 9H), 7.15-7.26 (m, 3H), 7.39(d, 1H, J = 8.6 Hz), 7.47-7.53 (m, 3H), 7.93 (d, 1H, J = 2.3 Hz), 8.28-8.30 (m, 1H), 8.67-8.70 (m, 1H), 9.89 (brs, 1H).

Application Example 17

^{1}H−NMR ($CDCl_3$) δ ppm : 1.32 (s, 9H), 1.37 (s, 9H), 7.14-7.216(m, 3H), 7.35-7.39 (m, 2H), 7.47-7.51 (m, 2H), 7.57-7.60 (m, 2H), 8.25-8.28 (m,1H), 8.69-8.73 (m, 1H), 9.80 (brs, 1H).

Application Example 18

^{1}H−NMR ($CDCl_3$) δ ppm : 2.92 (s, 6H), 6.39-6.43 (m, 2H), 6.51-6.55 (m, 1H), 6.89 (d, 1H, J = 8.9 Hz), 7.17-7.23 (m, 1H), 7.53 (d, 1H,J = 8.6 Hz), 7.67-7.71 (m, 1H), 7.97 (d, 1H, J = 2.0 Hz), 8.11-8.15 (m,2H), 8.23 (d, 1H, J = 2.6 Hz).

Application Example 19

^{1}H−NMR ($CDCl_3$) δ ppm : 1.35 (s, 9H), 2.94 (s, 6H), 6.42-6.48(m, 2H), 6.53-6.57 (m, 1H), 6.90 (d, 1H, J = 8.6 Hz), 7.19-7.25 (m, 1H),7.48-7.51 (m, 2H), 7.82-7.93 (m, 2H), 7.89 (brs, 1H), 8.19-8.25 (m, 2H).

Application Example 20

^{1}H−NMR (CDCl$_3$) δ ppm : 1.32 (s, 9H), 6.54 (brs, 1H), 6.89 (d,1H, J = 8.9 Hz), 7.22-7.26 (m, 2H), 7.34-7.38 (m, 2H), 7.57 (d, 1H, J =8.6 Hz), 7.68-7.72 (m, 2H), 7.88-7.92 (m, 1H), 7.97 (d, 1H, J = 2.6 Hz), 8.25 (d, 1H, J = 2.6 Hz).

Application Example 21

^{1}H−NMR (CDCl$_3$) δ ppm : 1.32 (s, 9H), 1.35 (s, 9H), 6.51 (brs,1H), 6.90 (d, 1H, J = 8.9 Hz), 7.22-7.25 (m, 2H), 7.33-7.37 (m, 2H), 7.49-7.52 (m, 2H), 7.70 (brs, 1H), 7.80-7.83 (m, 2H), 7.97 (dd, 1H, J = 2.6 Hz, 8.9 Hz), 8.25 (d, 1H, J = 2.6 Hz).

Application Example 22

^{1}H−NMR (CDCl3) δ ppm : 1.35 (s, 9H), 7.05-7.14 (m, 3H), 7.46(d, 2H), 7.58 (d, 1H), 7.71 (dd, 1H), 7.90 (dd, 1H), 8.02 (d, 1H), 8.48(brs, 1H), 8.84 (dd, 1H).

Application Example 23

^{1}H−NMR (CDCl$_3$) δ ppm : 1.30 (s, 9H), 1.34 (s, 18H), 7.05-7.13(m, 3H), 7.44 (d, 2H), 7.64 (t, 1H), 7.71 (d, 2H), 7.89 (dd, 1H), 8.52(brs, 1H), 8.89 (dd, 1H).

Application Example 24

^{1}H−NMR (CDCl$_3$) δ ppm : 2.67-2.71 (m, 2H), 2.93-2.97 (m, 2H),7.09-7.14 (m, 1H), 7.42-7.49 (m, 2H), 7.61 (d, 1H), 7.70-7.76 (m, 2H), 7.85 (dd, 1H), 8.03 (d, 1H), 8.44 (brs, 1H), 8.87 (d, 1H).

Application Example 25

^{1}H−NMR (CDCl$_3$) δ ppm : 1.37 (s, 18H), 2.67-2.72 (m, 2H), 2.96-3.01 (m, 2H), 7.10-7.15 (m, 1H), 7.45-7.48 (m,2H), 7.65-7.73 (m, 4H), 7.84 (dd, 1H), 8.50 (brs, 1H), 8.92 (dd, 1H).

Application Example 26

^{1}H−NMR (CDCl$_3$) δ ppm : 2.66-2.70 (m, 2H), 2.96-3.00 (m, 2H), 3.06 (s, 6H), 6.71 (d, 2H), 7.03 (d, 1H), 7.36-7.43 (m, 2H), 7.63 (d, 1H), 7.68 (brs, 1H), 7.78 (d, 2H), 8.19 (d, 1H), 8.30 (dd, 1H).

Application Example 27

^{1}H−NMR (CDCl$_3$) δ ppm : 2.60-2.64 (m, 2H), 2.84-2.86 (m, 2H), 3.84 (s, 6H), 7.10 (d, 1H), 7.17 (d, 1H), 7.44-7.65 (m, 5H), 8.23 (dd, 1H), 8.49 (d, 1H), 10.28 (brs, 1H).

Application Example 28

^{1}H−NMR (CDCl$_3$) δ ppm : 2.58 (s, 3H), 6.99-7.02 (m, 2H), 7.19-7.22 (m, 1H), 7.42 (t, 1H, J = 7.9 Hz), 7.51-7.54 (m, 2H), 7.58-7.61 (m, 2H), 7.66-7.71 (m, 2H), 7.96 (d, 1H, J = 2.0 Hz), 8.14 (brs, 1H).

Application Example 29

^{1}H−NMR (CDCl$_3$) δ ppm : 2.57 (s, 3H), 7.01-7.05 (m, 2H), 7.18-7.22 (m, 1H), 7.39-7.45 (m, 1H), 7.48-7.57 (m, 4H), 7.62-7.68 (m, 3H), 7.86 ? 7.89 (m, 2H), 7.95 (brs, 1H).

Application Example 30

^{1}H−NMR (CDCl$_3$) δ ppm : 2.12-2.17 (m, 2H), 2.64 (t, 2H), 2.96(t, 2H), 6.98-7.07 (m, 3H), 7.33-7.41 (m, 3H), 7.61 (brs, 1H), 8.07 (d,1H), 8.28 (d, 1H), 8.45 (dd, 1H).

Application Example 31

^{1}H−NMR (DMSO-d$_6$) δ ppm : 2.63-2.66 (m, 2H), 2.83-2.86 (m, 2H), 3.74 (s, 3H), 3.75 (s, 3H), 6.93(d, 1H), 7.29 (d, 2H), 7.43 (brs, 1H), 7.52-7.59 (m, 3H), 8.40 (dd, 1H), 8.67 (brs, 1H), 10.18 (brs, 1H).

Application Example 32
^{1}H−NMR ($CDCl_3$) δ ppm : 2.08-2.17 (m, 2 H), 2.64-2.68 (m, 2H).2.91-2.95 (m, 2H), 6.91-6.97 (m, 2H), 7.10 (d, 1H, J = 8.0 Hz), 7.24-7.30 (m, 1H), 7.54 (d, 1H, J = 8.2 Hz), 7.57-7.60 (m, 2H), 7.68-7.72 (m, 1H), 7.85(d, 1H, J = 7.6 Hz), 7.96 (d, 1H, J = 2.0 Hz), 8.05 (brs, 1H).

Application Example 33
^{1}H−NMR ($CDCl_3$) δ ppm : 2.09-2.18 (m, 2 H), 2.64-2.69 (m, 2H).2.92-2.96 (m, 2H), 6.94-6.98 (m, 2H), 7.09-7.11 (m, 1H), 7.25-7.31 (m, 1H), 7.47-7.62 (m, 5H), 7.80 (brs, 1H), 7.84-7.89 (m, 3 H).

Application Example 34
^{1}H−NMR ($CDCl_3$) δ ppm : 2.69-2.73 (m, 2H), 3.04-3.09 (m, 2H), 7.02-7.05 (m, 2H), 7.11(d, 1H, J = 7.9 Hz), 7.31-7.37 (m, 1H), 7.54 (d, 1H,J = 8.9 Hz), 7.59-7.64 (m, 3H), 7.69-7.73 (m, 1H), 7.88 (brs, 1H), 7.98(d, 1H,J = 1.6 Hz).

Application Example 35
^{1}H−NMR ($CDCl_3$) δ ppm : 2.64-2.73 (m, 2H), 3.05-3.09 (m, 2H), 7.02-7.06 (m, 2H), 7.09-7.12 (m, 1H), 7.31-7.36 (m, 1H), 7.47-7.57 (m, 4H),7.60 -7.66 (m, 2H), 7.83 (m, 1H), 7.86-7.89 (m, 2H).

Application Example 36
^{1}H−NMR ($CDCl_3$) δ ppm : 2.70-2.74 (m, 2H), 3.13-3.15 (m, 2H), 3.93(s, 6H), 6.87-6.90 (m, 1H), 6.96-7.00 (m, 1H), 7.36-7.40 (m, 1H), 7.42-7.44 (m, 2H), 7.48-7.50 (m, 2H), 8.14 (brs, 1H), 8.23-8.25 (m, 2H).

Application Example 37
^{1}H−NMR ($CDCl_3$) δ ppm : 2.33 (s, 6H), 2.72-2.76 (m, 2H), 3.12-3.16(m, 2H), 7.00 (d, 1H, J =

8.9 Hz), 7.23-7.26 (m, 1H), 7.37-7.41 (m, 1H), 7.47-7.52 (m, 2H), 7.58-7.61 (m, 1H), 7.66 (m, 1H), 7.84 (brs, 1H), 8.22-8.23 (m, 1H), 8.26-8.30 (m, 1H).

Application Example 38

^{1}H-NMR (DMSO-d_6) δ ppm : 2.00-2.02 (m, 2H), 2.27 (s, 3H), 2.39 (s, 3H), 2.58-2.68 (m, 2H), 2.84-2.90 (m, 2H), 7.10 (d, 1H), 7.44 (brs, 1H), 7.83 (d, 1H), 7.94 (dd, 1H), 8.18-8.22 (m, 2H), 8.39 (d, 1H), 10.53 (brs, 1H).

Application Example 39

^{1}H-NMR (DMSO-d_6) δ ppm : 1.97 -2.27 (m, 2H), 2.27 (s, 3H), 2.39 (s, 3H), 2.52-2.58 (m, 2H), 2.84-2.90 (m, 2H), 7.10 (d, 1H), 7.44 (brs, 1H), 7.59-7.69 (m, 1H), 7.84-7.88 (m, 1H), 7.98-8.06 (m, 1H), 8.19 (dd, 1H), 8.38 (d, 1H), 10.44 (brs, 1H).

Application Example 40

^{1}H-NMR (DMSO-d_6) δ ppm : 2.68-2.72 (m, 2H), 3.09-3.13 (m, 2H), 7.16 (d, 1H, J = 8.9 Hz), 7.29 (d, 1H, J = 2.0 Hz), 7.44-7.48 (m, 1H), 7.50 (d, 1H, J = 8.6 Hz), 7.64 (d, 1H, J = 8.3 Hz), 8.21-8.29 (m, 2H), 8.48(d, 1H, J = 2.3 Hz), 8.64 (d, 1H, J = 2.0 Hz), 10.73 (s, 1H).

Application Example 41

^{1}H-NMR (DMSO-d_6) δ ppm : 2.71-2.76 (m, 2H), 3.11-3.16 (m, 2H), 3.68 (s, 2H), 6.92-6.95 (m, 1H), 7.17-7.21 (m, 1H), 7.34-7.38 (m, 2H), 7.41-7.51 (m, 4H), 8.06-8.10 (m, 2H).

Application Example 42

^{1}H-NMR ($CDCl_3$) δ ppm : 2.71-2.76 (m, 2H), 3.12-3.17 (m, 2H), 3.96(s, 3H), 7.00-7.04 (m, 1H), 7.37-7.41 (m, 1H), 7.46 (d, 1H, J = 2.3 Hz), 7.51 (d, 1H, J = 8.6 Hz), 7.93-7.97 (m, 2H), 8.12-8.16 (m, 3H), 8.26-8.30 (m, 2H).

Application Example 43

^{1}H−NMR (DMSO-d_6) δ ppm : 2.58 (s, 3H), 7.19 -7.25 (m, 3H), 7.79-7.84 (m, 1H), 7.99-8.03 (m, 3 H), 8.27-8.32 (m, 3H), 8.58 (d, 1H), 10.70 (s, 1 H).

Application Example 44

^{1}H−NMR ($CDCl_3$) δ ppm : 2.10-2.15 (m, 2H), 2.49 (s, 3H), 2.90-2.95(m, 4H), 6.95-7.01 (m, 2H), 7.67 (brs, 1H), 7.74 (d, 2H), 7.99 (d, 2H),8.07 (brs, 1H), 8.21 (dd, 1H), 8.27 (d, 1H).

Application Example 45

^{1}H−NMR (DMSO-d_6) δ ppm : 2.04-2.09 (m, 2H), 2.41 (s, 3H), 2.87-2.93 (m, 4H), 7.02 (s, 1H), 7. 12 (d, 1H), 7.63 (brs, 1H), 7.83 (d, 1H), 7.94 (d d, 1H), 8.19 (d, 1H), 8.22 (d, 1H), 8.43 (d, 1H), 10.53 (s, 1H).

Application Example 46

^{1}H−NMR (DMSO-d_6) δ ppm : 2.58 (s, 3H), 7.18 -7.24 (m, 3H), 7.74-7.89 (m, 4H), 8.02 (d, 2H), 8. 24 (dd, 1H), 8.50 (d, 1H), 10.83 (brs, 1H).

Application Example 47

^{1}H−NMR ($CDCl_3$) δ ppm : 1.43 (d, 3H, J = 6.9 Hz), 2.20-2.28 (m, 1H), 2.83-2.92 (m, 1H), 3.45- 3.49 (m, 1H), 6.93 (d, 1H, J = 9.0 Hz), 7.04(d, 1 H, J = 7.9 Hz), 7.36 (d, 1H, J = 7.6 Hz), 7.51 (d, 1H, J = 9.0 Hz),7.62-7.68 (m, 1H), 7.74-7.78 (m, 1H), 7.99-8.04 (m, 2H), 8.21 (d, 1H, J= 2.6 Hz), 8.59 (brs, 1H).

Application Example 48

^{1}H−NMR ($CDCl_3$) δ ppm : 2.13 (s, 3H), 2.33 (s, 3H), 6.87-6.94 (m,2H), 7.02-7.05 (m, 1H), 7.07 (m, 1H), 7.56 (d, 1H, J = 8.3 Hz), 7.68-7.71 (m, 1H), 7.84 (brs, 1H), 7.97 (d, 1H, J = 2.3 Hz), 8.1 2-8.17 (m, 1H),8.19 (d, 1H, J = 2.3 Hz).

Application Example 49

^{1}H−NMR ($CDCl_3$) δ ppm : 2.13 (s, 3H), 2.33 (s, 3H), 6.89-6.95 (m, 2H), 7.02-7.05 (m, 1H), 7.08 (brs, 1H), 7.74-7.77 (m, 2H), 7.88 (brs, 1H), 7.97-8.00 (m, 2H), 8.17-8.21 (m, 2H).

Application Example 50

^{1}H−NMR ($CDCl_3$) δ ppm : 2.36 (s, 3H), 2.66-2.70 (m, 2H), 2.96-3.00(m, 2H), 6.94 (s, 1H), 7.35-7.38 (m, 1H), 7.41-7.47 (m, 1H), 7.53 (brs, 1H), 7.66 (d, 1H, J = 8.3 Hz), 7.63-7.67 (m, 1H), 7.71-7.75 (m, 1H), 8.00 (d, 1H, J = 2.0 Hz), 8.26 (s, 1H).

Application Example 51

^{1}H−NMR ($CDCl_3$) δ ppm : 2.37 (s, 3H), 2.65-2.70 (m, 2H), 2.96-3.00(m, 2H), 6.94 (s, 1H), 7.36 (dd, 1H, J = 1.0 Hz, 7.9 Hz), 7.41-7.47 (m, 1H), 7.64 (dd, 1H, J = 1.0 Hz, 7.3 Hz), 7.70 (brs, 1H), 7.76-7.79 (m, 2H), 8.01-8.04 (m, 2H), 8.29 (s, 1H).

Application Example 52

^{1}H−NMR ($CDCl_3$) δ ppm : 2.11 (s, 3H), 2.79 (s, 4H), 7.00-7.06 (m, 3H), 7.24 (d, 2H), 7.84 (d, 1H), 7.95 (dd, 1H), 8.18 (dd, 1H), 8.22 (d, 1H), 8.47 (d, 1H), 10.55 (s, 1H).

Application Example 53

^{1}H−NMR (DMSO-d_6) δ ppm : 2.11 (s, 3H), 2.79 (s, 4H), 7.00-7.06 (m, 3H), 7.24 (dd, 2H), 7.93 (d, 2H), 8.15-8.23 (m, 3H), 8.50 (d, 1H), 10.62 (s, 1H).

Application Example 54

^{1}H−NMR (DMSO-d_6) δ ppm : 2.11 (s, 3H), 2.39 (s, 3H), 2.79 (s, 4H), 6.99-7.03 (m, 3H), 7.23 (d, 2H), 7.35 (d, 2H), 7.88 (d, 2H), 8.20 (dd, 1H), 8.48 (d, 1H), 10.31 (s, 1H).

Application Example 55

^{1}H−NMR (DMSO-d_6) δ ppm : 2.98 (s, 3H), 2.81 (s, 4H), 7.09 (dd, 2H), 7.14 (d, 1H), 7.28 (dd, 2H), 7.63 (d, 1H), 7.72 (dd, 1H), 8.12 (d, 1H), 8.34 (dd, 1H), 8.69 (d, 1H), 10.54 (s, 1H).

Application Example 56

^{1}H−NMR (DMSO-d_6) δ ppm : 2.12 (s, 3H), 2.81 (s, 4H), 7.09 (dd, 2H), 7.15 (d, 1H), 7.28 (dd, 2H), 7.74 (d, 2H), 7.98 (d, 2H), 8.36 (dd, 1H), 8.72 (d, 1H), 10.62 (s, 1H).

Application Example 57

^{1}H−NMR ($CDCl_3$) δ ppm : 1.22 (t, 3H, J = 7.6 Hz), 2.29 (s, 3H), 2.57-2.66 (m, 2H), 6.88-6.94 (m, 3H), 7.15-7.18 (m, 1H), 7.57 (d, 1H, J =8.3 Hz), 7.68-7.72 (m, 1H), 7.83 (brs, 1H), 7.97 (d, 1H, J = 2.3 Hz), 8.13-8.18 (m, 1H), 8.23 (d, 1H, J = 2.3 Hz).

Application Example 58

^{1}H−NMR ($CDCl_3$) δ ppm : 1.22 (t, 3H, J = 7.6 Hz), 2.29 (s, 3H), 2.61 (q, 2H, J = 7.6 Hz), 6.87-6.95 (m, 3H), 7.15-7.18 (m, 1H), 7.73-7.77(m, 2H), 7.95 (brs, 1H), 7.97-8.00 (m, 2H), 8.16-8.21 (m, 1H), 8.25 (d,1H, J = 2.3 Hz).

Application Example 59

^{1}H−NMR ($CDCl_3$) δ ppm : 2.34 (s, 3H), 2.60 (s, 3H), 6.91 (s, 1H),7.17-7.22 (m, 3H), 7.58 (d, 1H), 7.72-7.75 (m, 2H), 7.98-8.03 (m, 3H), 8.31 (s, 1H).

Application Example 60

^{1}H−NMR ($CDCl_3$) δ ppm : 2.36 (s, 3H), 2.60 (s, 3H), 6.92 (s, 1H),7.19-7.23 (m, 2H), 7.74 (brs, 1H), 7.76-7.79 (m, 2H), 7.98-8.04 (m, 4H),8.37 (s, 1H).

Application Example 61

^{1}H−NMR ($CDCl_3$) δ ppm : 6.92-6.95 (m, 1H), 7.11-7.14 (m, 2H), 7.16-7.22 (m, 1H), 7.36-7.42 (m, 2H), 7.45-7.59 (m, 3H), 7.85-7.88 (m, 2H), 7.95 (brs, 1H), 8.21-8.25 (m, 2H).

Application Example 62

^{1}H−NMR ($CDCl_3$) δ ppm : 2.09 (s, 3H), 2.29 (s, 3H), 2.32 (s, 3H), 6.75 (s, 1H), 6.88-6.91 (m, 1H), 7.03-7.06 (m, 1H), 7.10-7.16 (m, 1H), 7.56-7.59 (m, 2H), 7.69-7.73 (m, 1H), 7.99 (d, 1H, J = 2 Hz), 8.22 (s, 1H).

Application Example 63

^{1}H−NMR ($CDCl_3$) δ ppm : 2.09 (s, 3H), 2.30 (s, 3H), 2.32 (s, 3H), 6.76 (s, 1H), 6.88-6.91 (m, 1H), 7.03-7.06 (m, 1H), 7.10-7.16 (m, 1H), 7.66 (brs, 1H), 7.75-7.78 (m, 2H), 7.99-8.02 (m, 2H), 8.26 (s, 1H).

Application Example 64

^{1}H−NMR ($CDCl_3$) δ ppm : 2.01 (s, 3H), 2.75-2.83 (m, 4H), 6.90 (d, 1H), 7.02 (dd, 1H), 7.15-7.29 (m, 3H), 7.55 (d, 1H), 7.71 (dd, 1H), 7.97 (d, 1H), 8.15 (dd, 2H), 8.24 (d, 1H).

Application Example 65

^{1}H−NMR (DMSO-d_6) δ ppm : 2.05 (s, 3H), 2.65-2.74 (m, 4H), 7.00-7.09 (m, 2H), 7.13-7.34 (m, 3H), 7.93 (d, 2H), 8.16 (d, 2H), 8.22 (dd, 1H), 8.47 (d, 1H), 10.62 (s, 1H).

Application Example 66

^{1}H−NMR (DMSO-d_6) δ ppm : 2.62-2.67 (m, 2H), 2.85-2.89 (m, 2H), 7.20 (d, 1H), 7.42-7.54 (m, 3H), 7.73-7.88 (m, 4H), 8.21 (d, 1H), 8.39 (d, 1H), 10.78 (s, 1H).

Application Example 67

^{1}H−NMR (DMSO-d_6) δ ppm : 2.63-2.67 (m, 2H), 2.85-2.89 (m, 2H), 7.21 (d, 1H), 7.44-7.55 (m, 3H), 7.78-7.84 (m, 1H), 7.99 (d, 1H), 8.25-8.31 (m, 3H), 8.50 (d, 1H), 10.66 (s, 1H).

Application Example 68

^{1}H−NMR ($CDCl_3$) δ ppm : 2.58 (s, 3H), 6.97-7.03 (m, 2H), 7.07-7.12(m, 2H), 7.57 (d, 1H, J = 8.6 Hz), 7.64-7.67 (m, 2H), 7.70-7.73 (m, 1H), 7.91-7.98 (m, 4H).

Application Example 69

^{1}H−NMR ($CDCl_3$) δ ppm : 2.58 (s, 3H), 6.97-7.03 (m, 2H), 7.09-7.13(m, 2H), 7.66-7.70 (m, 2H), 7.76-7.79 (m, 2H),7.90 (brs, 1H), 7.92-7.98(m, 2H), 7.99-8.02 (m, 2H).

Application Example 70

^{1}H−NMR ($CDCl_3$) δ ppm : 3.73 (s, 3H), 3.76 (s, 3H), 6.64 (dd, 1H),6.79 (d, 1H), 6.95-7.01 (m, 2H), 7.84 (d, 1H), 7.95 (dd, 1H), 8.16 (dd,1H), 8.22 (d, 1H), 8.47 (d, 1H), 10.54 (brs, 1H).

Application Example 71

^{1}H−NMR ($CDCl_3$) δ ppm : 2.60 (s, 3H), 7.07-7.10 (m, 2H), 7.11-7.16(m, 2H), 7.41-7.50 (m, 2H), 7.83 (brs, 1H), 7.86-7.91 (m, 3H), 7.97-8.02 (m, 2H).

Application Example 72

^{1}H−NMR ($CDCl_3$) δ ppm : 2.60 (s, 3H), 7.06-7.12 (m, 2H), 7.13-7.18(m, 2H), 7.62-7.66 (m, 2H), 7.77-7.80 (m, 2H), 7.89-7.94 (m, 3H), 7.97-8.03 (m, 2H).

Application Example 73

^{1}H−NMR ($CDCl_3$) δ ppm : 2.24 (s, 6H), 6.82-

6.86 (m, 1H), 6.89-6.93(m, 2H), 7.13 (d, 1H, J = 7.9 Hz), 7.55 (d, 1H, J = 8.2 Hz), 7.67-7.71(m, 1H), 7.96-7.97 (m, 2H), 8.12-8.16 (m, 1H), 8.21 (d, 1H, J = 2.6 Hz).

Application Example 74

^{1}H-NMR ($CDCl_3$) δ ppm : 2.24 (s, 6H), 6.82-6.86 (m, 1H), 6.89-6.93(m, 2H), 7.13 (d, 1H, J = 7.9 Hz), 7.72-7.75 (m, 2H), 7.96-7.99 (m, 2H), 8.02 (brs, 1H), 8.15-8.19 (m, 1H), 8.23 (d, 1H, J = 2.3 Hz).

Application Example 75

^{1}H-NMR (DMSO-d_6) δ ppm : 1.12 (s, 6H), 2.74 (s, 2H), 7.19 (d, 1H), 7.47-7.57 (m, 3H), 7.85 (d, 1H), 7.96 (dd, 1H), 8.23-8.28 (m, 2H), 8.47 (d, 1H), 10.59 (brs, 1H).

Application Example 76

^{1}H-NMR (DMSO-d_6) δ ppm : 2.0 (s, 3H), 2.7 (s, 4H), 6.9 (m, 2H), 7.0 (m, 2H), 7.3 (t, 1H), 7.8 (d, 1H), 7.9 (dd, 1H), 8.2 (m, 2H), 8.5 (d,1H), 10.5 (s, 1H).

Application Example 77

^{1}H-NMR ($CDCl_3$) δ ppm : 2.64-2.68 (m, 2H), 2.92-2.96 (m, 2H), 3.69(s, 2H), 6.98 (d, 1H, J = 8.6 Hz), 7.18-7.21 (m, 2H), 7.31-7.33 (m, 1H), 7.39-7.48 (m, 3H), 7.63 (d, 1H, J = 7.3 Hz), 8.06-8.11 (m, 2H).

Application Example 78

^{1}H-NMR ($CDCl_3$) δ ppm : 2.63-2.67 (m, 2H), 2.91-2.95 (m, 2H), 3.80(s, 2H), 6.97 (d, 1H, J = 8.6 Hz), 7.29-7.33 (m, 1H), 7.38-7.48 (m, 4H), 7.60-7.65 (m, 3H), 8.06-8.12 (m, 2H).

Application Example 79

^{1}H−NMR (DMSO-d_6) δ ppm : 2.64 (t, 2H), 2.86 (t, 2H), 7.22 (d, 1H), 7.46-7.53 (m, 3H), 8.19-8.23 (m, 1H), 8.38 (d, 1H), 11.22 (s, 1H).

Application Example 80

^{1}H−NMR (DMSO-d_6) δ ppm : 2.27 (s, 6H), 2.64 (t, 2H), 2.88 (t, 2H), 7.10-7.28 (m, 4H), 7.42-7.54 (m, 3H), 8.24 (dd, 1H), 8.44 (d, 1H), 10.55 (s, 1H).

Application Example 81

^{1}H−NMR (DMSO-d_6) δ ppm : 2.64 (m, 2H), 2.86 (m, 2H), 3.76 (s, 6H), 6.74 (d, 2H), 7.14 (d, 1H), 7.34-7.54 (m, 4H), 8.23 (dd, 1H), 8.43 (d, 1H), 10.42 (s, 1H).

Application Example 82

^{1}H−NMR ($CDCl_3$) δ ppm : 2.15 (s, 3H), 2.74-2.81 (m, 2H), 2.88-2.93(m, 2H), 6.95-6.98 (m, 3H), 7.02 (d, 1H), 7.26-7.34 (m, 1H), 7.76 (d, 2H), 7.88 (brs, 1H), 8.00 (d, 2H), 8.21 (dd, 1H), 8.21 (d, 1H).

Application Example 83

^{1}H−NMR (DMSO-d_6) δ ppm : 2.61 (t, 2H), 2.83 (t, 2H), 3.75 (s, 6H), 6.88 (d, 1H), 7.13 (d, 1H), 7.39-7.49 (m, 2H), 7.63 (d, 1H), 8.18 (dd, 1H), 8.36 (d, 1H), 10.59 (s, 1H).

Application Example 84

^{1}H−NMR (DMSO-d_6) δ ppm : 2.65 (t, 2H), 2.88 (t, 2H), 3.83 (s, 6H), 7.20 (d, 1H), 7.42-7.56 (m, 3H), 7.86 (s, 1H), 8.22 (dd, 1H), 8.39 (d, 1H), 10.83 (s, 1H).

Application Example 85

^{1}H-NMR ($CDCl_3$) δ ppm: 2.74 (m, 2H), 3.05 (m, 2H), 3.38 (s, 3H), 4.52 (s, 2H), 6.99 (d, 1H, J=9Hz), 7.55 (m, 4H), 7.80 (d, 1H, J=7Hz), 8.14 (s, 1H), 8.20 (d, 1H, J=8Hz), 9.25 (d, 1H, J=9Hz), 9.37 (s, 1H), 10.59 (s, 1H).

Application Example 86

^{1}H-NMR (DMSO-d_6) δ ppm: 2.62-2.67 (m, 2H), 2.84-2.88 (m, 2H), 7.23 (d, 1H, J = 9 Hz), 7.46-7.53 (m, 4H), 8.24-8.28 (m, 1H), 8.41-8.49 (m, 2H), 8.74 (d, 1H, J = 2 Hz), 10.90 (s, 1H).

Application Example 87

^{1}H-NMR ($CDCl_3$) δ ppm: 2.00 (s, 3H), 6.83-6.90 (m, 3H), 6.92-6.96(m, 1H), 7.28-7.35 (m, 1H), 7.47 (d, 1H, J = 8 Hz), 7.63-7.67 (m, 1H),7.91 (d, 1H, J = 2 Hz), 8.05-8.10 (m, 1H), 8.22 (d, 1H, J = 3 Hz), 8.63(brs, 1H).

Application Example 88

Production of pentafluoro-N1-[6-[(2,3-dihydro-2,2-dimethyl-1-oxo-1H-inden-4-yl)oxy]-3-pyridinyl]benzamide

(Step 1) Production of 4-[(5-amino-2-pyridinyl)oxy]-2,2-dimethyl-1-indanone

0.20 g of sodium hydride (60%), 1.00 g of 4-[(5-amino-2-pyridinyl)oxy]-1- indanone produced in the same way as in Reference Example 2, and 1 mL of iodomethane were added sequentially to 30 mL of THF and stirred for 3 h at room temperature. The reaction solution was poured into water and extracted with ethyl acetate. The organic layer was washed with a 10% potassium carbonate aqueous solution followed by saturated saline, and then dried on anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The oily residue was refined by silica gel column chromatography (eluent: ethyl acetate: hexane = 1:1) to obtain 0.83 g of the title compound.

^{1}H-NMR($CDCl_3$) (ppm: 1.21 (s, 6H), 2.83 (s,

2 H), 3.56 (brs, 2 H), 6.83 (dd, 1 H), 7.13 (dd, 1 H), 7.25 (dd, 1 H), 7.34-7.40 (m, 1 H), 7.57 (d, 1 H), 7.68 (d, 1 H).

(Step 2) Production of pentafluoro-N1-[6-[(2,3-dihydro-2,2-dimethyl-1-oxo-1H-inden-4-yl)oxy]-3-pyridinyl]benzamide

0.32 g of the 4-[(5-amino-2-pyridinyl)oxy]-2,2-dimethyl-1-indanone produced in Step 1 was dissolved in 10 mL of THF, and 0.13 g of pentafluorobenzoyl chloride followed by 0.13 mL of triethylamine were added while cooling. After stirring for 1 h at the same temperature, the reaction solution was extracted with ethyl acetate. The organic layer was washed with 1N hydrochloric acid followed by saturated saline and dried on anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The oily residue was crystallized from a mixture of ethyl acetate and ether to obtain 0.30 g of the title compound as a white powder.

[0217]

^{1}H-NMR ($CDCl_3$) δ ppm : 1.21 (s, 6H), 2.82 (s, 2H), 7.06 (d, 1H), 7.35-7.45 (m, 2 H), 7.63-7.65 (m, 1H), 7.85 (brs, 1H), 8.20 (d, 1 H), 8.27 (dd, 1H).

The compounds of Application Examples 89-112 below were produced by the same method as in Application Example 88.

Application Example 89

Production of 3,4-dichloro-N1-[2-[(1-oxo-2,3-dihydro-1H-inden-4-yl)oxy]pyrimidin-5-yl]benzamide

0.20 g of the 4-[(5-aminopyrimidin-2-yl)oxy]indanon-1-one produced in Reference Example 4 was dissolved in 10 mL of tetrahydrofuran, and 0.21 g of 3,4-dichlorobenzoyl chloride followed by 0.13 mL of triethylamine were added while cooling and stirred for 1 h at the same temperature. The reaction mixture was partitioned with ethyl acetate-water (50 mL each). The organic layer was washed sequentially with 1% hydrochloric acid, a saturated sodium bicarbonate aqueous solution, and saturated saline, and dried on anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The solid residue was recrystallized from a mixed solvent of ethyl acetate and n-hexane to obtain 0.21 g of the title compound. A very light yellow, crystalline powder.

[0218]

^{1}H-NMR ($DMSO-d_6$) δ ppm :

2.65(t, 2H), 2.88(t, 2H), 7.52-7.60(m, 3H), 7.86(d, 1H), 7.96(dd, 1H), 8.23(d, 1H), 8.96(s, 2H), 10.75(s, 1H).

Application Example 90

Production of 5-[4-[(3,4-dichlorobenzoyl)amino]phenoxy]-3,4-dihydronaphthalen-1-yl acetate

0.17 g of the 5-(4-aminophenoxy)-3,4-dihydronaphthalen-1-yl acetate produced in Reference Example 7 was dissolved in 10 mL of tetrahydrofuran, and 0.13 g of 3,4-dichlorobenzoyl chloride and 88 μL of triethylamine were added dropwise while cooling. After stirring for 30 min at the same temperature, the solution was diluted by 30 mL of ethyl acetate, washed sequentially with 1N hydrochloric acid, saturated sodium bicarbonate aqueous solution, and saturated saline, and dried on anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The solid obtained was recrystallized from ethyl acetate-n-hexane to obtain 0.26 g of the title compound. White powder.

[0219]

^{1}H-NMR ($CDCl_3$) δ ppm: 2.32 (s, 3H), 2.39-2.47 (m, 2H), 2.85 (t, 2H), 5.74 (t, 1H), 6.85 (d, 1H), 6.92-6.95 (m, 3H), 7.12-7.18 (m, 1H), 7.52-7.59 (m, 3H), 7.70 (dd, 2H), 7.97 (d, 1H).

Application Example 91

^{1}H-NMR (DMSO-d_6) δ ppm: 2.62-2.65 (m, 2H), 2.83-2.86 (m, 2H), 3.32 (s, 3H), 3.33 (s, 3H), 6.67 (d, 1H), 7.02 (d, 1H), 7.14-7.22 (m, 3H), 7.40-7.58 (m, 4H), 8.22 (dd, 1H), 8.41 (brs, 1H), 10.33 (brs, 1H).

Application Example 92

^{1}H-NMR ($CDCl_3$) δ ppm: 2.66-2.70 (m, 2H), 2.96-3.01 (m, 2H), 7.08(d, 1H), 7.26-7.44 (m, 5H), 7.63 (m, 2H), 8.20 (d, 1H), 8.33 (dd, 1H).

Application Example 93

^{1}H−NMR ($CDCl_3$) δ ppm : 7.15 (d, 1H), 7.35-7.39 (m, 1H), 7.47 (d, 1H), 7.58-7.72 (m, 4H), 7.98 (d, 1H), 8.14 (dd, 1H), 8.54 (d, 1H).

Application Example 94

^{1}H−NMR ($CDCl_3$) δ ppm : 3.85 (s, 3H), 7.17 (d, 1H, J = 9 Hz), 7.43-7.47 (m, 1H), 7.56-7.62 (m, 2H), 7.78-7.86 (m, 2H), 7.93-7.97 (m, 1H), 8.22-8.27 (m, 2H), 8.50 (d, 1H, J = 2 Hz), 10.60 (s, 1H).

Application Example 95

^{1}H−NMR (DMSO-d_6) δ ppm : 2.60-2.65 (m, 2H), 2.82-2.86 (m, 2H), 3.28 (s, 3H), 7.07 (d, 1H, J = 9 Hz), 7.35-7.49 (m, 4H), 7.64 (d, 1H, J =9 Hz), 7.70 (d, 1H, J = 3 Hz), 7.94 (dd, 1H, J = 3 Hz, 9 Hz), 8.15 (d, 1H, J = 3 Hz), 8.56 (s, 1H).

Application Example 96

^{1}H−NMR (DMSO-d_6) δ ppm : 2.62-2.66 (m, 2H), 2.84-2.88 (m, 2H), 7.19 (d, 1H, J = 9 Hz), 7.45-7.52 (m, 3H), 8.03-8.13 (m, 4H), 8.26 (dd, 1H, J= 3 Hz, 9 Hz), 8.49 (d, 1H, J = 3 Hz), 10.66 (s, 1H).

Application Example 97

^{1}H−NMR (DMSO-d_6) δ ppm : 2.62-2.66 (m, 2H), 2.84-2.88 (m, 2H), 3.31 (s, 3H), 7.17 (d, 1H, J = 9 Hz), 7.35 (d, 1H, J = 8 Hz), 7.44-7.52 (m,4H), 7.88 (d, 2H, J = 8 Hz), 8.26 (dd, 1H, J = 3 Hz, 9 Hz), 8.49 (d, 1H, J = 3 Hz), 10.34 (s, 1H).

Application Example 98

^{1}H-NMR ($CDCl_3$) δppm: 2.68 (t, 2H, J=6Hz), 2.98 (t, 3H, J=6Hz), 3.92 (s, 3H), 3.94 (s, 6H), 7.06 (d, 1H, J=8Hz), 7.09 (s, 2H), 7.44 (t, 1H, J=7.5Hz), 7.65 (d, 1H, J=7.5Hz), 7.77 (s, 1H), 8.25 (d, 1H, J=8Hz), 8.25 (s, 1H).

Application Example 99

^{1}H-NMR (DMSO-d_6) δppm: 1.99-2.03 (m, 2H), 2.61 (t, 2H), 2.71 (t, 2H), 7.41-7.49 (m, 2H), 7.81-7.87 (m, 2H), 7.95 (dd, 1H), 8.22 (d, 1H), 8.94 (s, 2H), 10.75 (s, 1H).

Application Example 100

^{1}H-NMR (DMSO-d_6) δppm: 2.25 (s, 3H), 2.27 (s, 3H), 6.96 (d, 1H, J=9Hz), 7.26 (m, 2H), 7.36 (s, 1H), 7.83 (d, 1H, J=8Hz), 7.93 (dd, 1H, J=8Hz, 2Hz), 8.00 (dd, 1H, J=9Hz, 3Hz), 8.21 (d, 1H, J=2Hz), 8.76 (d, 1H, J=3Hz), 10.58 (s, 1H).

Application Example 101

^{1}H-NMR (DMSO-d_6) δppm: 2.25 (s, 3H), 2.27 (s, 3H), 6.97 (d, 1H, J=8.5Hz), 7.25 (d, 1H, J=8Hz), 7.30 (d, 1H, J=8Hz), 7.36 (s, 1H), 7.93 (d, 2H, J=8Hz), 8.03 (dd, 1H, J=8.5Hz, 2Hz), 8.15 (d, 2H, J=8Hz), 8.79 (d, 1H, J=3Hz), 10.66 (s, 1H).

Application Example 102

^{1}H−NMR ($CDCl_3$) δ ppm : 2.09 (s, 3H), 2.05-2.14 (m, 1H), 2.47-2.56(m, 1H), 2.74-2.86 (m, 1H), 2.94-3.04 (m, 1H), 6.21-6.25 (m, 1H), 6.86-7.01 (m, 3H), 7.19-7.23 (m, 2H), 7.55-7.59 (m, 3H), 7.68-7.73 (m, 2H),7.97 (d, 1H).

Application Example 103

^{1}H−NMR (DMSO-d_6) δ ppm : 1.98-2.04 (m, 2H), 2.72 (t, 2H), 2.91 (t, 2H), 6.70 (d, 1H), 6.95 (dd, 2H), 7.05 (d, 1H), 7.12-7.18 (m, 1H), 7.71-7.75 (m, 2H), 7.82 (d, 1H), 7.94 (dd, 1H), 8.21 (d, 1H), 10.39 (s, 1H).

Application Example 104

^{1}H−NMR ($CDCl_3$) δ ppm : 2.35 (s, 3H), 3.34 (d, 2H,J=2.3Hz), 6.33 (t, 1H, J=2.3Hz), 6.85 (d, 1H, J=1.9Hz), 7.01-7.04 (m, 2H), 7.12 (d, 1H,J=7.3Hz), 7.29-7.33 (m, 1H), 7.55-7.60(m, 3H), 7.68-7.72 (m, 2H), 7.98 (d, 1H, J=1.9Hz).

Application Example 105

^{1}H−NMR (DMSO-d_6) δ ppm : 1.99-2.03 (m, 2H), 2.51-2.58 (m, 2H), 2.87-2.91 (m, 2H), 6.84-6.92 (m, 2H), 7.15 (d, 2H), 7.82-7.97 (m, 5H), 8.22 (d, 1H), 10.48 (s, 1H).

Application Example 106

^{1}H−NMR ($CDCl_3$) δ ppm : 2.05−2.16 (m、2H)、2.88 (t、4H)、6.80 (dd、1H)、6.88 (d、1H)、7.01 (d、2H)、7.17 (d、1H)、7.52−7.58 (m、3H)、7.67−7.73 (m、2H)、7.96 (d、1H)。

Application Example 107

^{1}H−NMR ($CDCl_3$) δppm：3．84（s、3H）、3．88（s、3H）、6．56（dd、1H）、6．65（d、1H）、6．83（d、1H）、6．99（d、2H）、7．51−7．59（m、3H）、7．68−7．73（m、2H）、7．97（d、1H）。

Application Example 108

^{1}H−NMR ($CDCl_3$) δppm：5．98（s、2H）、6．49（dd、1H）、6．58（d、1H）、6．76（d、1H）、6．98（d、2H）、7．52−7．58（m、3H）、7．69（dd、1H）、7．76（brs、1H）、7．96（d、1H）。

[0222]

Application Example 109

^{1}H−NMR ($CDCl_3$) δppm：2．93（s、6H）、6．33（dd、1H）、6．40−6．41（m、1H）、6．49（dd、1H）、7．04（d、2H）、7．15−7．20（m、1H）、7．53−7．58（m、3H）、7．68−7．72（m、2H）、7．97（d、1H）。

Application Example 110

^{1}H−NMR ($CDCl_3$) δppm：2．09−2．19（m、2H）、2．65（t、2H）、2．95（t、2H）、7．02（d、2H）、7．17（dd、1H）、7．25（d、1H）、7．56−7．61（m、4H）、7．71（dd、1H）、7．78（s、1H）、7．98（d、1H）。

[0223]

Application Example 111

^{1}H−NMR ($CDCl_3$) δppm：2.19 (s, 3 H), 3.71 (s, 2 H), 6.98 (d, 1 H, J=9 Hz), 7.11 (d, 2 H, J=8 Hz), 7.23 (d, 2 H, J=8 Hz), 7.77 (d, 2 H, J=8 Hz), 7.88 (s, 1 H), 7.99 (d, 2 H, J=8 Hz), 8.22 (dd, 1 H, J=2.5 Hz, 9Hz), 8.26 (d, 1 H, J=2.5 Hz).

Application Example 112

^{1}H−NMR (DMSO-d_6) δ ppm : 2.16 (s, 3 H), 3.79 (s, 2 H), 7.06 (d,2 H, J=8.5 Hz), 7.07 (d, 1 H, J=8.5 Hz), 7.22 (d, 2 H, J=8.5 Hz), 7.84 (d, 1 H, J=8.5 Hz), 7.96 (dd, 1 H, J=2.5 Hz, 8.5 Hz), 8.20 (dd, 1 H, J=2.5 Hz, 8.5 Hz), 8.24 (d, 1 H, J=2.5 Hz),8.49 (d, 1 H, J=2.5 Hz), 10.60 (s, 1 H).

Application Example 113

Production of N-[6-[4-(tert-butyl)phenoxy]pyridin-3-yl]-N'-(2,4-dimethoxyphenyl)urea

160 mg of 2,4-dimethoxyphenyl isocyanate was added to 5 mL of a tetrahydrofuran solution of 200 mg of 3-amino-6-[4-(tert-butyl)phenoxy]pyridine while cooling. The reaction solution was stirred for one day while gradually returning to room temperature. The reaction solution was concentrated under reduced pressure. The residue was refined by silica gel column to obtain 310 mg of the title compound.

[0224]

^{1}H−NMR ($CDCl_3$) δ ppm : 1.29 (s, 9H), 3.72 (s, 3H), 3.77 (s,3H), 6.43-6.46 (m, 2H), 6.83 (d, 1H, J = 8.6 Hz), 6.94 (brs,1H), 6.99 (d, 2H, J = 8.2 Hz), 7.26 (m, 1H), 7.35 (d, 2H, J = 8.2 Hz), 7.75-7.78 (m,1H), 7.94 (m, 1H), 7.98-8.02 (m, 1H).

The compounds of Application Examples 114-131 below were produced by the same method as in Application Example 113.

[0225]

Application Example 114

^{1}H−NMR (DMSO-d_6) δ ppm : 2.49-2.51 (m, 2H), 2.61-2.66 (m, 2H), 3.71 (s, 3H), 6.84-6.90 (m, 2 H), 7.10 (d, 1H), 7.32-7.52 (m, 5H), 8.25 (dd, 1 H), 8.16 (d, 1H), 8.58 (brs, 1H), 8.70 (brs, 1H).

Application Example 115

^{1}H−NMR ($CDCl_3$) δ ppm : 3.73 (s, 3H), 3.76 (s, 3H), 6.60 (dd, 1H), 6.77 (d, 1H), 6.91-6.97 (m, 2H), 7.35 (dd, 1H), 7.52 (d, 1H), 7.87 (d, 1H), 7.94 (dd, 1H), 8.18 (d, 1H), 8.95 (brs, 1H), 9.17 (brs, 1H).

Application Example 116

^{1}H−NMR (DMSO-d_6) δ ppm : 2.66 (t, 2H, J = 6 Hz), 3.00 (t, 2H, J =6 Hz), 7.03 (d, 2H, J = 9 Hz), 7.10 (m, 1H), 7.30-7.55 (m, 4H), 7.50 (d, 2H, J = 9 Hz), 7.88 (s, 1H), 8.94 (m, 1H), 9.09(m, 1H).

Application Example 117

^{1}H−NMR (DMSO-d_6) δ ppm : 2.05 (m, 2H), 2.62 (t, 2H, J = 6 Hz), 2.88 (t, 2H, J = 6 Hz), 6.94 (d, 2H, J = 9 Hz), 7.09 (d, 1H, J = 8 Hz), 7.32 (d, 1H, J = 8 Hz), 7.34 (d, 1H, J = 8 Hz), 7.47 (d, 2H, J = 9 Hz), 7.51 (d, 1H, J = 8 Hz), 7.68 (d, 1H, J = 8 Hz), 7.88 (s, 1H), 8.96 (s, 1H)9.13 (s, 1H).

Application Example 118

^{1}H−NMR (DMSO-d_5) δ ppm : 2.62-2.66 (m, 2H), 2.84-2.88 (m, 2H), 7.12 (d, 1H, J = 9 Hz), 7.17 (brs, 1H), 7.38-7.54 (m, 5H), 8.03 (dd, 1H, J= 3 Hz, 9 Hz), 8.18 (d, 1H, J = 3 Hz), 8.98 (brs, 1H), 9.15 (brs, 1H).

Application Example 119

^{1}H−NMR (DMSO-d_6) δ ppm : 2.62-2.66 (m, 2H), 2.85-2.89 (m, 2H), 7.14 (d, 1H, J = 9 Hz), 7.37-7.53 (m, 7H), 7.98 (dd, 1H, J = 3 Hz, 9 Hz), 8.08 (d, 1H, J = 3 Hz), 9.80 (brs, 1H), 9.99 (brs, 1H).

Application Example 120

^{1}H−NMR (DMSO-d_6) δ ppm : 2.62-2.66 (m, 2H), 2.84-2.88 (m, 2H), 7.09-7.16 (m, 2H), 7.39-7.53 (m, 4H), 8.08 (dd, 1H, J = 3 Hz, 9 Hz), 8.16(d, 1H, J = 3 Hz), 8.30 (d, 1H, J = 3 Hz), 8.53 (s, 1H), 9.61 (s, 1H).

Application Example 121

^{1}H-NMR (DMSO-d_6) δ ppm: 2.70 (m, 4H), 5.06 (s, 1H), 5.55 (s, 1H), 6.95 (d, 1H, J=8Hz), 7.00 (d, 1H, J=8Hz), 7.26 (t, 1H, J=8Hz), 7.35 (dd, 1H, J=9Hz, 3Hz), 7.41 (d, 1H, J=9Hz), 7.52 (d, 1H, J=9Hz), 7.86 (d, 1H, J=3Hz), 7.98 (dd, 1H, J=9Hz, 3Hz), 8.16 (d, 1H, J=3Hz), 9.03 (s, 1H), 9.23 (s, 1H).

Application Example 122

^{1}H-NMR (DMSO-d_6) δ ppm: 2.64 (t, 2H, J=6Hz), 2.86 (t, 2H, J=6Hz), 7.12 (d, 1H, J=9Hz), 7.27 (d, 2H, J=9Hz), 7.35-7.55 (m, 3H), 7.56 (d, 2H, J=9Hz), 8.03 (dd, 1H, J=9Hz, 3Hz), 8.18 (d, 1H, J=3Hz), 8.99 (s, 1H), 9.13 (s, 1H).

Application Example 123

^{1}H-NMR (DMSO-d_6) δ ppm: 2.64 (t, 2H, J=6Hz), 2.88 (t, 2H, J=6Hz), 7.15 (d, 1H, J=9Hz), 7.40-7.55 (m, 4H), 7.58 (d, 1H, J=9Hz), 7.88 (s, 1H), 7.98 (dd, 1H, J=9Hz, 3Hz), 8.09 (d, 1H, J=3Hz), 10.09 (brs, 2H).

Application Example 124

^{1}H-NMR (DMSO-d_6) δ ppm: 7.10 (d, 1H, J = 9 Hz), 7.17 (dd, 2H, J= 2 Hz, 7 Hz), 7.47 (dd, 2H, J = 2 Hz, 7 Hz), 7.55 (d, 1H, J = 9 Hz), 7.69-7.73 (m, 1H), 8.02-8.06 (m, 2H), 8.35 (d, 1H, J = 3 Hz), 9.76 (s, 1H), 10.91 (s, 1H).

Application Example 125

^{1}H-NMR (DMSO-d_6) δ ppm : 3.76 (s, 3H), 6.92 -7.06 (m, 5H), 7.32-7.36 (m, 1H), 7.51 (d, 1H, J = 9Hz), 7.86 (d, 1H, J = 2 Hz), 7.94 (dd, 1H, J = 3 Hz, 9 Hz), 8.15 (d, 1H, J = 2 Hz), 8.84 (s, 1H), 9.06 (s, 1H).

Application Example 126

^{1}H-NMR (DMSO-d_6) δ ppm : 1.99-2.03 (m, 2H), 2.58-2.63 (m, 2H), 2.68-2.73 (m, 2H), 7.35-7.44 (m, 3H), 7.53 (d, 1H), 7.80-7.83 (m, 1H), 7.86 (d, 1H), 8.70 (s, 2H), 8.99 (s, 1H), 9.28 (s, 1H).

[0226]

Application Example 127

^{1}H-NMR (DMSO-d_6) δ ppm : 2.64 (t, 2H), 2.86 (t, 2H), 7.37 (dd, 1H), 7.50-7.58 (m, 4H), 7.86 (d, 1H), 8.72 (s, 2H), 9.00 (s, 1H), 9.26 (s, 1H).

Application Example 128

^{1}H-NMR (DMSO-d_6) δ ppm : 2.88 (s, 6H), 6.75 (dd, 2H), 6.87 (d, 1H), 6.94 (dd, 2H), 7.32-7.36 (m, 1H), 7.52 (d, 1H), 7.87 (d, 1H), 7.91 (dd, 1H), 8.14 (d, 1H), 8.82 (s, 1H), 9.06 (s, 1H).

Application Example 129

^{1}H-NMR (DMSO-d_6) δ ppm : 2.06 (s, 3H), 3.75 (s, 3H), 6.75-6.93 (m, 4H), 7.32-7.36 (m, 1H), 7.51 (d, 1H), 7.86 (d, 1H), 7.93 (dd, 1H), 8.10 (d, 1H), 8.80 (s, 1H), 9.06 (s, 1H).

Application Example 130

^{1}H-NMR (DMSO-d_6) δ ppm : 5.98 (s, 2H), 6.69 -6.87 (m, 3H), 7.03 (d, 1H), 7.35 (dd, 1H), 7.52 (d, 1H), 7.86 (d, 1H), 7.97 (dd, 1H), 8.15 (d, 1 H), 8.87 (s, 1H), 9.08 (s, 1H).

Application Example 131

^{1}H-NMR (DMSO-d_6) δ ppm : 3.99 (s, 3 H), 7.0 2 (d, 1 H, J=7 Hz), 7.10 (d, 1 H, J=9 Hz), 7.22 (d, 1 H, J=7 Hz), 7.34 (dd, 1 H, J=3 Hz, 9 Hz), 7. 41-7.53 (m, 4 H), 7.86 (d, 1 H, J=2 Hz), 7.98-8.03 (m, 2 H), 8.11 (d, 1 H, J=2 Hz), 8.87 (s, 1 H), 9.09 (s, 1 H).

Application Example 132

Production of 2-[(4-acetyl)phenoxy]-5-benzoylpyridine

(Step 1) Production of 2-chloro-5-[(N-methoxy-N-methyl)carbamoyl]pyridine

2.0 g of 6-chloronicotinic acid was dissolved in 10 mL of N,N-dimethylformamide, and 1.3 g of N,O-dimethylhydroxylamine hydrochloride, 2.7 g of water-soluble carbodiimide, and 2.0 mL of triethylamine were added while cooling and stirred for 24 h at room temperature. The reaction solution was extracted with ethyl acetate, washed sequentially with water, a saturated sodium bicarbonate aqueous solution, and saturated saline, and dried on anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The oily residue was refined by silica gel column chromatography (eluent: ethyl acetate: hexane = 1:1) to obtain 2.32 g of the title compound. Light brown oil.

[0227]

^{1}H-NMR ($CDCl_3$) δ ppm : 3.39 (s, 3H), 3.56 (s, 3H), 7.38-7.41 (m,1H), 8.00-8.05 (m, 1H), 8.78 (d, 1H, J = 1.7 Hz).

(Step 2) Production of 5-benzoyl-2-chloropyridine

140 mg of magnesium were added to 6 mL of a tetrahydrofuran (THF) solution of 850 mg of bromobenzene at room temperature in an argon gas atmosphere. After stirring for 2 h, 6 mL of a THF solution of 1.0 g of the 2-chloro-5-[(N-methoxy-N- methyl)carbamoyl]pyridine produced in step 1 were added dropwise in an argon gas atmosphere while cooling to -20°C and stirred for 2 h at the same temperature and for another h at room temperature. 50 mL of saturated ammonium chloride aqueous solution were added while cooling and stirring, and the solution

was extracted with ethyl acetate. The extract was washed sequentially with water, a saturated sodium bicarbonate aqueous solution, and saturated saline, and dried on anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The oily residue was refined by silica gel column chromatography (eluent: ethyl acetate: hexane = 1:1) to obtain 770 mg of the title compound. Very light yellow oil.

[0228]

^{1}H−NMR ($CDCl_3$) δ ppm : 7.47-7.5
6 (m, 3H), 7.63-7.68 (m, 1H), 7.78-7.82 (m, 2H),
8.08-8.12 (m, 1H), 8.78 (d, 1H, J = 2.3 Hz).

(Step 3) Production of 2-[(4-acetyl)phenoxy]-5-benzoyl pyridine

The title compound was obtained in the same way as in Reference Example 1 using the 5-benzoyl-2-chloropyridine produced in Step 2 and 4-hydroxyacetophenone. White powder.

[0229]

^{1}H−NMR ($CDCl_3$) δ ppm : 2.62 (s,
3H), 7.09-7.13 (m, 1H), 7.26-7.31 (m, 2H), 7.47-
7.53 (m, 2H), 7.58-7.64 (m, 1H), 7.77-7.81 (m, 2
H), 8.03-8.09 (m, 2H), 8.24-8.28 (m, 1H), 8.59-8.6
0 (m, 1H).

The compounds of Application Examples 133-140 below were produced by the same method as in Application Example 132.

Application Example 133

^{1}H−NMR ($CDCl_3$) δ ppm : 2.67-2.71 (m, 2H),
2.72-3.01 (m, 2H), 7.14(d, 1H, J = 8.3 Hz), 7.40-
7.43 (m, 1H), 7.45-7.52 (m, 3H), 7.58-7.62 (m, 1
H), 7.68-7.72 (m, 1H), 7.77-7.81 (m, 2H), 8.25-8.2
9 (m, 1H), 8.56-8.57 (m, 1H).

Application Example 134

^{1}H−NMR ($CDCl_3$) δ ppm : 2.61 (s, 3H), 7.11-
7.15 (m, 4H), 7.57-7.65(m, 2H), 7.82-7.85 (m, 2H),
7.89 (d, 1H), 8.00-8.03 (m, 2H).

Application Example 135

^{1}H−NMR ($CDCl_3$) δ ppm : 2.62 (s, 3H), 7.12 (dd, 1H), 7.26-7.31 (m, 2H), 7.57-7.65 (m, 2H), 7.89 (d, 1H), 8.05-8.09 (m, 2H), 8.23 (dd, 1H), 8.57 (d, 1H).

Application Example 136

^{1}H−NMR ($CDCl_3$) δ ppm : 2.68-2.72 (m, 2H), 2.96-3.00 (m, 2H), 7.17 (d, 1H), 7.27-7.64 (m, 4H), 7.70 (d, 1H), 7.88 (d, 1H), 8.24 (dd, 1H), 8.54 (d, 1H).

Application Example 137

^{1}H−NMR ($CDCl_3$) δ ppm : 2.70 (m, 2 H), 2.96 (m, 2 H), 7.17 (d, 1 H, J=8 Hz), 7.42 (t, 1 H, J=8 Hz), 7.50 (d, 1 H, J=8 Hz), 7.71 (d, 1 H, J=8 Hz), 7.77 (d, 2 H, J=8 Hz), 7.88 (d, 2 H, J=8 Hz), 8.27 (dd, 1 H, J=2Hz, 8 Hz), 8.55 (d, 1 H, J=2 Hz).

Application Example 138

^{1}H NMR ($CDCl_3$) δ ppm : 1.67 (s, 3H), 3.76-3.81 (m, 2H), 4.05-4.10 (m, 2H), 7.05-7.09 (m, 2H), 7.31 (d, 1H, J = 3 Hz), 7.50 (d, 1H, J = 9Hz), 7.60-7.63 (m, 2H), 7.75-7.78 (m, 2H), 8.22-8.26 (m, 1H), 8.57 (d, 1H, J = 2 Hz).

Application Example 139

^{1}H−NMR ($CDCl_3$) δ ppm : 1.67 (s, 3H), 3.75-3.81 (m, 2H), 4.05-4.10 (m, 2H), 7.10 (d, 1H, J = 9 Hz), 7.30-7.33 (m, 2H), 7.60-7.63 (m, 2H), 7.69-7.72 (m, 2H), 7.75-7.78 (m, 2H), 8.23-8.28 (m, 1H), 8.58-8.59 (m, 1H).

Application Example 140

^{1}H−NMR ($CDCl_3$) δ ppm : 2.70(m, 2 H), 2.96 (m, 2 H), 7.17 (d, 1 H, J=8 Hz), 7.42 (t, 1 H, J=8 Hz), 7.50 (d, 1 H, J=8 Hz), 7.71 (d, 1 H, J=8 Hz), 7.77 (d, 2 H, J=8 Hz), 7.88 (d, 2 H, J=8 Hz), 8.27 (dd, 1 H, J=2Hz, 8 Hz), 8.55 (d, 1 H, J=2 Hz).

Application Example 141

Production of Z-1-[4-(4-acetylphenoxy)phenyl]-2-(3,4-dichlorophenyl)ethene

0.5 mL of concentrated hydrochloric acid was added while cooling to 5 mL of a THF solution of 500 mg of Z-1-(3,4-dichlorophenyl)-2-[4-[4-(1,3-dioxolan-2-yl)phenoxy]phenyl]ethene. The reaction solution was stirred for 15 min at 0°C. After rendering the reaction solution alkaline by adding sodium bicarbonate while cooling, it was extracted with ethyl acetate. The ethyl acetate layer was washed with a saturated sodium bicarbonate aqueous solution and saturated saline, and then dried on anhydrous magnesium sulfate. The solvent was distilled off and the residue was refined by silica gel column chromatography (n-hexane/ethyl acetate = 5/1) to obtain 420 mg of the title compound.

[0230]

^{1}H−NMR ($CDCl_3$) δ ppm : 2.58 (s, 3H), 6.48 (d, 1H, J = 12.2 Hz), 6.66 (d, 1H, J = 12.2 Hz), 6.93-6.98 (m, 2H), 7.00-7.03 (m, 2H), 7.06-7.10 (m, 1H), 7.21-7.26 (m, 2H), 7.29-7.32 (m, 2H), 7.93-7.96 (m, 2H).

The compounds of Application Examples 142-147 below were produced by the same method as in Application Example 141.

Application Example 142

^{1}H−NMR ($CDCl_3$) δ ppm : 2.67 (s, 3H), 7.05-7.12 (m, 2H), 7.34 (d, 1H, J = 2.6 Hz), 7.50 (d, 1H, J = 8.9 Hz), 7.84-7.87 (m, 2H), 8.05-8.09 (m, 2H), 8.23-8.28 (m, 1H), 8.56-8.57 (m, 1H).

Application Example 143

^{1}H−NMR ($CDCl_3$) δ ppm : 2.63 (s, 3H), 7.13 (d, 1H, J = 8.6 Hz), 7.30-7.33 (m, 2H), 7.69-7.73 (m, 2H), 7.84-7.87 (m, 2H), 8.05-8.08 (m, 2H), 8.25-8.29 (m, 1H), 8.58 (d, 1H, J = 2.0 Hz).

Application Example 144

^{1}H−NMR ($CDCl_3$) δ p p m : 2.63 (s, 3H), 7.12 (d, 1H), 7.26-7.47 (m,2H), 7.60 (d, 1H), 7.70-7.81 (m, 4H), 7.84 (d, 1H), 8.04-8.08 (m, 2H), 8.40 (d d, 1H), 8.87 (d, 1H).

Application Example 145

^{1}H−NMR ($CDCl_3$) δ p p m : 2.59 (s, 3H), 7.02-7.10 (m, 5H), 7.19 (d,1H, J = 16.2 Hz), 7.53-7.58 (m, 2H), 7.61 (m, 4H), 7.94-7.99 (m, 2H).

Application Example 146

^{1}H−NMR ($CDCl_3$) δ p p m : 2.58 (s, 3H), 6.94 (d, 1H, J = 16.2 Hz), 7.02-7.34 (m, 6H), 7.42 (d, 1H, J = 8.3 Hz), 7.51-7.54 (m, 2H), 7.59 (d,1H, J = 2.0 Hz), 7.94-7.98 (m, 2H).

Application Example 147

^{1}H−NMR ($CDCl_3$) δ p p m : 2.58 (s, 3H), 6.60 (d, 1H, J = 13 Hz), 6.69 (d, 1H, J = 13 Hz), 6.92-6.95 (m, 2H), 7.00-7.04 (m, 2H), 7.21-7.25 (m, 2 H), 7.35-7.38 (m, 2H), 7.49-7.52 (m, 2H), 7.93-7.9 7 (m, 2H).

Application Example 148

Production of 4-methyl-N-{[2-(7-methyl-2,3-dihydro-1H-inden-4-yl)oxy]pyridin-3-yl}benzene sulfonamide

160 mg of 4-methylbenzene sulfonyl chloride were added while cooling to 2 mL of a pyridine solution of 200 mg of 3-amino-2-[(7-methyl-2,3-dihydro-1H-inden-4- yl)oxy]pyridine. The reaction solution was stirred for 18 h while gradually returning to room temperature. The reaction solution was concentrated under reduced pressure, and ethyl acetate and a saturated sodium bicarbonate aqueous solution were added to the residue. The ethyl acetate layer was separated, washed with a saturated sodium bicarbonate aqueous solution and saturated saline, and dried on anhydrous magnesium sulfate. The solvent was distilled off. The residue was refined by silica gel column chromatography (eluent: n-hexane/ethyl acetate = 5/1) to obtain 290 mg of the title compound.

[0231]

^{1}H−NMR (CDCl$_3$) δ ppm : 1.92 -1.97 (m, 2H), 2.22 (s, 3H), 2.31(t, 2H, J = 7.6 Hz), 2.40 (s, 3H), 2.80-2.85 (m, 2H), 6.47 (d, 1H, J =7.9 Hz), 6.90-6.95 (m, 2H), 7.07 (brs, 1H), 7.23-7.26 (m, 2H), 7.69 (d,2H, J = 8.2 Hz), 7.80 (dd, 1H, J = 1.6 Hz, 4.9 Hz), 7.95 (dd, 1H, J = 1.6 Hz, 7.9 Hz).

The compounds of Application Examples 149-160 below were produced by the same method as in Application Example 148.

[0232]

Application Example 149

Production of N-[6-(4-tert-butylphenoxy)pyridin-3-yl]-3,4-dimethoxybenzene sulfonamide

(473 mg of 3,4-dimethoxybenzenesulfonyl chloride were added to 10 mL of a pyridine solution of 484 mg of 3-amino-6-[(4-tert-butyl)phenoxy]pyridine and stirred for 6 h at room temperature. The reaction solution was concentrated. Ethyl acetate was added to the residue, and it was washed sequentially with 10% hydrochloric acid, saturated saline, a saturated sodium bicarbonate aqueous solution, and saturated saline. The ethyl acetate solution was dried on anhydrous magnesium sulfate, and the solvent was distilled off. The residue was crystallized by ether to obtain 650 mg of the title compound.)

^{1}H−NMR (CDCl$_3$) δ ppm : 1.32 (s, 9H), 3.83 (s, 3H), 3.92 (s,3H), 6.46 (brs, 1H), 6.82-6.88 (m, 2H), 7.01 (d, 2H), 7.15 (d, 1H), 7.03-7.41 (m, 3H), 7.58 (dd, 1H), 7.75 (d, 1H).

Application Example 150

^{1}H−NMR (CDCl$_3$) δ ppm : 1.93-1.98 (m, 2H), 2.22 (s, 3H), 2.30-2.36 (m, 2H), 2.79-2.85 (m, 2H), 3.78 (s, 3H), 3.92 (s, 3H), 6.48 (d, 1H), 6.85 (d, 1H), 6.91-6.96 (m, 2H), 7.05 (brs, 1H), 7.20-7.25 (m, 1H), 7.42 (dd, 1H), 7.82 (dd, 1H), 7.97 (dd, 1H).

Application Example 151

^{1}H−NMR ($CDCl_3$) δ ppm : 1.85-1.96 (m, 2 H), 2.22 (s, 3H), 2.53(t, 2H, J = 7.6 Hz), 2.79-2. 85 (m, 2H), 6.71 (d, 1H, J = 7.9 Hz), 6.83 (d, 1H, J = 15.5 Hz), 6.93-6.98 (m, 2H), 7.02 (brs, 1H), 7.36-7.43 (m, 5H), 7.51 (d, 1H, J = 15.5 Hz), 7.85 (dd, 1H, J = 1.6 Hz, 4.9 Hz), 7.89-7.92 (m, 1H).

Application Example 152

^{1}H−NMR ($CDCl_3$) δ ppm : 1.32 (s, 9H), 6. 46 (brs, 1H), 6.78 (d,1H, J = 15.5 Hz), 6.88 (d, 1 H, J = 8.6 Hz), 7.01-7.04 (m, 2H), 7.37-7.47 (m, 8 H), 7.67-7.71 (m, 1H), 8.03 (d, 1H, J = 3.0 Hz).

Application Example 153

^{1}H−NMR ($CDCl_3$) δ ppm : 1.32 (s, 9H), 6. 84 (d, 1H, J = 8.9 Hz), 6.98-7.02 (m, 3H), 7.37-7. 40 (m, 2H), 7.46-7.47 (m, 2H), 7.60-7.64 (m,1H), 7.85 (d, 1H, J = 2.6 Hz), 7.90 (m, 1H).

Application Example 154

^{1}H−NMR ($CDCl_3$+DMSO-d_6) δ ppm : 2.64-2.68 (m, 2H), 2.86-2.91 (m, 2H), 6.89-6.92 (m, 1H), 7.2 8-7.31 (m, 1H), 7.38-7.43 (m, 3H), 7.60-7.66 (m, 2 H), 7.69-7.72 (m, 2H), 7.82 (m, 1H), 9.22 (brs, 1 H).

Application Example 155

^{1}H−NMR (DMSO-d_6) δ ppm : 2.59-2.61 (m, 2H), 2.69-2.71 (m, 2H), 7.08-7.11 (m, 1H), 7.37-7.40 (m, 1H), 7.43-7.52 (m, 2H), 7.60-7.64 (m, 1H), 7.7 0-7.79 (m, 2H), 7.84-7.85 (m, 1H), 7.92-7.95 (m, 1 H), 10.81 (brs, 1H).

Application Example 156

^{1}H−NMR (DMSO-d_6) δ ppm : 2.58-2.62 (m, 2H), 2.70-2.74 (m, 2H), 7.05-7.09 (m, 1H), 7.36-7.39 (m, 1H), 7.43-7.49 (m, 2H), 7.52-7.65 (m, 4H), 7.70-7.77 (m, 3H), 10.31 (brs, 1H).

Application Example 157

^{1}H−NMR ($CDCl_3$) δ ppm : 1.16 (d, 12H, J = 7 Hz), 1.23 ($_{d6}$H, J = 7Hz), 2.62-2.66 (m, 2H), 2.86-2.90 (m, 3H), 3.87-3.96 (m, 2H), 6.30 (brs,1H), 6.96-6.99 (m, 1H), 7.12 (s, 2H), 7.25-7.26 (m, 1H), 7.28-7.40 (m,1H), 7.43-7.65 (m, 3H).

Application Example 158

^{1}H−NMR (DMSO-d_6) δ ppm : 1.99 (s, 3H), 2.50-2.62 (m, 2H), 2.70-2.72 (m, 2H), 7.05-7.37 (m, 1H), 7.39-7.54 (m, 3H), 7.55-7.58 (m, 1H), 7.61-7.64 (m, 2H), 7.70-7.75 (m, 3H), 10.17 (brs, 1H), 10.33 (brs, 1H).

Application Example 159

^{1}H−NMR ($CDCl_3$) δ ppm : 2.65-2.70 (m, 2H), 2.87-2.91 (m, 2H), 6.99(d, 1H, J = 9 Hz), 7.31 (d, 1H, J = 8 Hz), 7.38-7.43 (m, 1H), 7.62 (d,1H), 7.67-7.78 (m, 3H), 7.97 (brs, 1H), 8.06-8.10 (m, 1H), 8.38-8.42 (m,1H), 8.56 (m, 1H).

Application Example 160

^{1}H−NMR ($CDCl_3$) δ ppm : 2.65-2.70 (m, 2H), 2.88-2.92 (m, 2H), 6.63(brs, 1H), 7.00-7.03 (m, 1H), 7.32-7.35 (m, 1H), 7.41-7.47 (m, 1H), 7.55-7.56 (m, 2H), 7.65-7.71 (m, 3H), 7.80-7.81 (m, 1H).

Application Example 161

(Step 1) Production of (2,3-dimethylphenyl)-(5-nitropyridin-2-yl)amine

2-Chloro-5-nitropyridine (2.4 g) and an acetic acid solution (5 mL) of 2,3-xylidine (2.02 g) were heated for 17 h at 100°C. Ethyl acetate and then a saturated sodium bicarbonate aqueous solution were added to the reaction solution, and the compound that precipitated was filtered out.

The compound that had been filtered out was washed with ethyl acetate and the title compound (intermediate compound) was obtained (3.04 g).

^{1}H-NMR (CDCl$_3$) δppm: 2.18 (s, 3H), 2.35 (s, 3H), 6.37 (d, 1H, J=9.5Hz), 7.06 (brs, 1H), 7.17 (s, 3H), 8.18 (dd, 1H, J=9.5Hz, 2.7Hz), 9.06 (d, 1H, J=2.7Hz).

The target compound of Application Example 161 was produced by the same method as in Application Example 113 using the compound obtained in Step 1.

^{1}H-NMR (DMSO-d$_6$) δppm: 1.99 (s, 3H), 2.09 (s, 3H), 6.60 (d, 1H, J=8Hz), 6.90 (d, 1H, J=8Hz), 7.02 (t, 1H, J=8Hz), 7.25 (d, 1H, J=8Hz), 7.32 (dd, 1H, J=9Hz, 2.5Hz), 7.50 (d, 1H, J=9Hz), 7.59 (dd, 1H, J=9Hz, 2.5Hz), 7.86 (d, 1H, J=2.5Hz), 8.00 (s, 1H), 8.05 (d, 1H, J=2.5Hz), 8.47 (s, 1H), 8.96 (s, 1H).

Application Example 162

The compound of Application Example 162 was produced by the same method as in Application Example 161 (final step by the method of Application Example 88).

^{1}H-NMR (DMSO-d$_6$) δppm: 2.10 (s, 3H), 2.27 (s, 3H), 6.63 (d, 1H, J=8Hz), 6.64 (d, 1H, J=9Hz), 7.05 (t, 1H, J=8Hz), 7.25 (d, 1H, J=8Hz), 7.84 (dd, 1H, J=9Hz, 2Hz), 8.16 (s, 1H), 7.91 (d, 2H, J=8Hz), 8.14 (d, 2H, J=8Hz), 8.36 (d, 1H, J=2Hz), 10.33 (s, 1H).

Application Example 163

(Step 1) Production of 6-(2,3-dimethylbenzyl)-3-pyridinylamine

2-(2,3-dimethylbenzoyl)-5-nitropyridine was suspended in 1,3-propanediol (4 mL). Hydrazine monohydrate (380 μL) and potassium hydroxide (730 mg) were added, and the

solution was heated for 7 h at 160°C. Ethyl acetate was added to the reaction solution, and it was washed with water and saturated saline. The organic layer was dried on magnesium sulfate and concentrated under reduced pressure. The residue obtained was refined by silica gel chromatography (chloroform: methanol = 50:1) to obtain the title compound (120 mg).
^{1}H-NMR ($CDCl_3$) δ ppm: 2.13 (s, 3H), 2.28 (s, 3H), 3.56 (brs, 2H), 4.09 (s, 2H), 6.72 (d, 1H, J=8.3Hz), 6.87 (dd, 1H, J=8.3Hz, 3.0Hz), 7.04 (m, 3H), 8.05 (d, 1H, J=3.0Hz).

The compound of Application Example 163 was produced by the same method as in Application Example 88 using the compound obtained in Step 1.
^{1}H-NMR (DMSO-d_6) δ ppm: 2.13 (s, 3H), 2.25 (s, 3H), 4.29 (s, 2H), 7.08 (m, 3H), 7.40 (d, 1H, J=8Hz), 7.87 (d, 1H, J=8Hz), 7.99 (dd, 1H, J=8Hz, 2Hz), 8.28 (d, 1H, J=2Hz), 8.38 (dd, 1H, J=8Hz, 2Hz), 9.08 (d, 1H, J=2Hz), 11.00 (s, 1H).

Application Example 164

The compound of Application Example 164 was obtained by the same method as in Application Example 163.
^{1}H-NMR (DMSO-d_6) δ ppm: 2.13 (s, 3H), 2.25 (s, 3H), 4.28 (s, 2H), 7.08 (m, 3H), 7.38 (d, 1H, J=9Hz), 7.96 (d, 2H, J=8Hz), 8.20 (d, 2H, J=8Hz), 8.38 (dd, 1H, J=9Hz, 2Hz), 9.09 (d, 1H, J=2Hz), 11.03 (s, 1H).

Application Example 165

(Step 1) Production of 6-{[1-(tert-butyldimethylsilanyloxy)-2,3-dihydro-1H-inden-4-yl]oxy}nicotinic acid

2N sodium hydroxide (5.6 mL) was added to a dioxane (20 mL) solution of ethyl 6-{[1-(tert-butyldimethylsilanyloxy)-2,3-dihydro-1H-inden-4-yl]oxy}nicotinate (2.32 g) and stirred for 2 h at 60°C. The reaction solution was cooled. 1N hydrochloric acid (11.2 mL) was added, and

the solution was extracted with ethyl acetate. The organic layer was concentrated under reduced pressure to obtain the title compound (2.16 g).

^{1}H-NMR (DMSO-d_6) δ ppm: 0.13 (s, 3H), 0.16 (s, 3H), 0.91 (s, 9H), 1.60-2.80 (m, 4H), 5.30 (t, 1H, J=7Hz), 6.97 (d, 1H, J=8Hz), 7.00 (d, 1H, J=8Hz), 7.12 (d, 1H, J=8Hz), 7.29 (t, 1H, J=8Hz), 8.22 (dd, 1H, J=8Hz, 2Hz), 8.60 (d, 1H, J=2Hz).

(Step 2) Synthesis of N-methoxy-N-methyl 6-[(1-(tert-butyldimethylsilanyloxy-2,3-dihydro-1H-inden-4-yl)oxy]nicotinamide

N,O-dimethylhydroxylamine hydrochloride (660 mg), 1-hydroxybenzotriazole (860 mg), 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (1.29 g), and triethylamine (1.96 mL) were added to a DMF (60 mL) solution of 6-[(1-(tert-butyldimethylsilanyloxy-2,3-dihydro-1H-inden-4-yl)oxy]nicotinic acid (216 g) and stirred for 5 h at room temperature. The reaction solution was concentrated under reduced pressure. Ethyl acetate was added, and the solution was washed with water and saturated saline. The organic layer was dried on magnesium sulfate and concentrated under reduced pressure. The residue obtained by refined by silica gel chromatography (hexane: ethyl acetate = 2:1) to obtain the title compound (1.92 g).

^{1}H-NMR ($CDCl_3$) δ ppm: 0.16 (s, 3H), 0.18 (s, 3H), 0.96 (s, 9H), 1.90 (m, 1H), 2.40 (m, 1H), 2.54 (m, 1H), 2.80 (dd, 1H, J=16Hz, 9Hz), 3.37 (s, 3H), 3.58 (s, 3H), 5.31 (t, 1H, J=7Hz), 6.89 (d, 1H, J=8.5Hz), 7.01 (d, 1H, J=7.5Hz), 7.22 (d, 1H, J=7.5Hz), 7.30 (t, 1H, J=7.5Hz), 8.08 (dd, 1H, J=8.5, 2Hz), 8.61 (d, 1H, J=2Hz).

(Step 3) Production of 1-{6-[1-(tert-butyldimethylsilanyloxy)indan-4-yloxy]-pyridin-3-yl}-2-(3,4-dichlorophenyl)-ethanone

A diethyl ether solution (5 mL) of 3,4-dichlorobenzyl chloride (740 mg) was added dropwise to a diethyl ether (4 mL) solution of magnesium (280 mg) and stirred for 10 min after dropwise addition had been completed. The reaction solution was added dropwise to a tetra[hydro]furan (10mL) solution of N-methoxy-N-methyl 6-[(1-(tert-butyldimethylsilanyloxy-2,3-dihydro-1H-inden-4-yl)oxy]nicotinamide. After stirring for 1 h at room temperature, the

solution was cooled and treated by saturated aqueous ammonium chloride. The reaction solution was concentrated under reduced pressure. Ethyl acetate was added, and it was washed with water and saturated saline. After drying on magnesium sulfate and concentrating under reduced pressure, the residue obtained was refined by silica gel chromatography (hexane: ethyl acetate = 7:1) to obtain the title compound (920 mg).

^{1}H-NMR ($CDCl_3$) δ ppm: 0.16 (s, 3H), 0.19 (s, 3H), 0.96 (s, 9H), 1.90 (m, 1H), 2.45 (m, 2H), 2.78 (m, 1H), 4.17 (s, 2H), 5.32 (t, 1H, J=7Hz), 6.97 (d, 1H, J=8Hz), 7.00 (d, 1H, J=7Hz), 7.08 (dd, 1H, J=8Hz, 2Hz), 7.20-7.33 (m, 2H), 7.35 (d, 1H, J=2Hz), 7.40 (d, 1H, J=8Hz), 8.26 (dd, 1H, J=8, 2Hz), 8.78 (d, 1H, J=2Hz).

(Step 4) Production of 1-{6-[1-hydroxyindan-4-yloxy]-pyridin-3-yl}-2-(3,4-dichlorophenyl)ethanone

A tetrahydrofuran solution (3.5 mL) of 1N tetrabutylammonium fluoride was added to a tetrahydrofuran (8 mL) solution of 1-{6-[1-(tert-butyldimethylsilanyloxy)indan-4-yloxy]-pyridin-3-yl}-2-(3,4-dichlorophenyl)ethanone (920 mg) and stirred for 5 h at room temperature. The reaction solution was concentrated under reduced pressure. Ethyl acetate was added, and it was washed with water and saturated saline. After drying on magnesium sulfate and concentrating under reduced pressure, the residue obtained was refined by silica gel chromatography (hexane: ethyl acetate = 5:1) to obtain the title compound (target compound) (250 mg).

^{1}H-NMR ($CDCl_3$) δ ppm: 1.94 (m, 2H), 2.55 (m, 2H), 2.85 (m, 1H), 4.16 (s, 2H), 5.31 (t, 1H, J=6.6Hz), 7.00 (d, 1H, J=9Hz), 7.07 (m, 2H), 7.35 (m, 3H), 8.28 (dd, 1H, J=9Hz, 2.5Hz), 8.77 (d, 1H, J=2.5Hz).

Application Example 166

(Step 1) Production of 2-(2,3-dimethylbenzoyl)-5-nitropyridine

2,3-Dimethylbenzene acetonitrile (4.72 g) and 2-chloro-5-nitropyridine (4.84 g) were dissolved in DMF (65 mL), substituted by argon, and cooled. Potassium t-butoxide (6.93 g) was

added to this solution, stirred for 1 h at room temperature, and cooled. 30% Aqueous hydrogen peroxide (10.4 mL) was added to this solution, which was gradually returned to room temperature over 3 h. The reaction solution was poured into 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed sequentially with a saturated sodium bicarbonate aqueous solution and saturated saline, dried on magnesium sulfate, and concentrated under reduced pressure. The residue obtained was refined by silica gel chromatography (hexane: ethyl acetate = 10:1) to obtain the title compound (890 mg).

^{1}H-NMR ($CDCl_3$) δppm: 2.24 (s, 3H), 2.36 (s, 3H), 7.19 (d, 2H, J=4.5Hz), 7.35 (t, 1H, J=4.5Hz), 8.31 (d, 1H, J=9Hz), 8.67 (dd, 1H, J=9Hz, 2Hz), 9.45 (d, 1H, J=2Hz).

The compound of Application Example 166 was produced by the same method as in Application Example 113 using the compound obtained in Step 1.

^{1}H-NMR (DMSO-d_6) δppm: 2.30 (s, 3H), 2.32 (s, 3H), 7.29 (d, 1H, J=8Hz), 7.39 (dd, 1H, J=9Hz, 2.5Hz), 7.56 (d, 1H, J=9Hz), 7.74 (d, 1H, J=8Hz), 7.76 (s, 1H), 7.90 (d, 1H, J=2.5Hz), 7.99 (d, 1H, J=9Hz), 8.19 (dd, 1H, J=9Hz, 2.5Hz), 8.72 (d, 1H, J=2.5Hz), 9.25 (s, 1

Application Example 167

The compound of Application Example 167 was produced by the same method as in Application Example 166 (final step according to the method of Application Example 88).

^{1}H-NMR (DMSO-d_6) δppm: 2.06 (s, 3H), 2.30 (s, 3H), 7.12 (d, 1H, J = 7Hz), 7.18 (t, 1H, J = 7 Hz), 7.31 (d, 1H, J = 7 Hz), 7.86 (d, 1H, J = 8 Hz), 7.97 (dd, 1H, J = 8 Hz, 1 Hz), 8.15 (d, 1H, J = 8 Hz), 8.25 (d, 1H, J = 1 Hz), 8.47 (dd, 1H, J = 8 Hz, 2 Hz), 8.93 (d, 1H, J = 2 Hz), 10.93 (s, 1 H).

Application Example 168

The compound of Application Example 167 [sic; 168] was produced by the same method as in Application Example 167.

^{1}H−NMR (DMSO-d_6) δ ppm : 2.06 (s, 3H), 2.30 (s, 3H), 7.13 (d, 1H, J = 7 Hz), 7.18 (t, 1H, J = 7 Hz), 7.31 (d, 1H, 7 Hz), 7.96 (d, 2H, J =9 Hz), 8.10 (d, 1H, J = 9 Hz), 8.19 (d, 2H, J = 9 Hz), 8.50 (dd, 1H, J= 9 Hz, 2 Hz), 8.95 (d, 1H, J = 2 Hz), 11.03 (brs, 1H).

Application Example 169

Production of 4-[5-[(3,4-dichlorobenzyl)amino]-2-pyridinyl]oxy]-1-indanone

0.96 g of 4-[(5-amino-2-pyridinyl)oxy]-1-indanone produced in the same way as in Reference Example 2 and 0.70 g of 3,4-dichlorobenzaldehyde were dissolved in a mixed solution of 40 mL of methanol and 60 mL of tetrahydrofuran, and 0.30 g of sodium cyanoborohydride was added. After stirring for 3 days at room temperature, the solvent was distilled off under reduced pressure. The oily residue was dissolved in ethyl acetate, washed with water, and dried on anhydrous sodium sulfate. Some solvent remained. The oily residue was refined by silica gel column chromatography (eluent: ethyl acetate: hexane = 1:4) to obtain 0.08 g of the title compound. White powder.

[0233]

^{1}H−NMR ($CDCl_3$) δ ppm : 2.58 (t, 2H), 3.00 (t, 2H), 4.05 (m, 1H), 4.30 (m, 2H), 6.86 (d, 1H), 7.02 (dd, 1H), 7.21 (dd, 1H), 7.23 (d, 1H), 7.34-7.46 (m, 3H), 7.56-7.58 (m, 2H).

The compounds of Application Examples 170-174 below were produced by the same method as in Application Example 169.

Application Example 170

^{1}H−NMR ($CDCl_3$) δ ppm : 1.31 (s, 9H), 1.32 (s, 9H), 3.90 (brs, 1H), 4.27 (s, 2H), 6.76 (d, 1H, J = 8.9 Hz), 6.95-7.04 (m, 3H), 7.26?7.39 (m, 6H), 7.67 (d, 1H, J = 3.0 Hz).

Application Example 171

^{1}H−NMR ($CDCl_3$) δ ppm : 1.31 (s, 9H), 4.29 (s, 2H), 6.76 (d, 1H, J = 8.9 Hz), 6.95-7.00 (m, 4H), 7.18-7.21 (m, 1H), 7.33-7.36 (m, 2H), 7.41 (d, 1H, J = 8.3 Hz), 7.46 (d, 1H, J = 2.0 Hz), 7.62 (d, 1H, J = 3.0 Hz).

Application Example 172

^{1}H−NMR ($CDCl_3$) δ ppm : 2.10 (s, 3H), 2.29 (s, 3H), 3.99 (brs, 1H), 4.24 (s, 2H), 6.67-6.70 (m, 1H), 6.79-6.82 (m, 1H), 6.92-6.96 (m, 1H), 6.98 (brs, 1H), 7.04-7.09 (m, 1H), 7.15-7.19 (m, 1H), 7.39 (d, 1H, J =8.2 Hz), 7.44 (d, 1H, J = 2.0 Hz), 7.56 (d, 1H, J = 3.0 Hz).

Application Example 173

^{1}H−NMR ($DMSO-d_6$) δ ppm : 1.98-2.06 (m, 2H), 2.51-2.56 (m, 2H), 2.82-2.88 (m, 2H), 3.72 (s, 3H), 3.74 (s, 3H), 4.19 (d, 2H), 6.38 (t, 1H), 6.82-6.90 (m, 5H), 6.99 (brs, 1H), 7.15 (dd, 1H), 7.63 (d, 1H), 7.84 (d, 1H).

Application Example 174

MS m/e 415(M+) for C26H29N3O2(415.53)

Application Example 175

Production of 3,4-dichloro-N1-[6-[(2-bromo-2,3-dihydro-1-oxo-1H-inden-4-yl)oxy]-3-pyridinyl]benzamide

2.00 g of 3,4-dichloro-N1-[6-[(2,3-dihydro-1-oxo-1H-inden-4-yl)oxy]-3-pyridinyl]benzamide was dissolved in a mixed solution of dioxane-THF-acetic acid (20 mL each). 1.55 g of pyridinium bromide perbromide were added and stirred for 2 h at 80°C. The reaction solution was introduced into a saturated sodium bicarbonate aqueous solution and extracted with ethyl acetate. The organic layer was washed with saturated saline and dried on anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The oily residue was refined by silica gel column chromatography (eluent: ethyl acetate: hexane = 1:2) to obtain 0.94 g of the title compound. White powder.

[0234]

^{1}H−NMR ($CDCl_3$) δ ppm : 3.25 (d
d, 1H), 3.67 (dd, 1H), 4.63 (dd, 1H), 7.07 (dd, 1
H), 7.26-7.59 (m, 3H), 7.70-7.74 (m, 2H), 7.97-7.9
9 (m, 2H), 8.23-8.28 (m, 2H).

Application Example 176

Production of 3,4-dichloro-N1-[6-[(2,3-dihydro-2-formyloxy-1-oxo-1H-inden-4-yl)oxy]-3-pyridinyl]benzamide

0.88 g of the 3,4-dichloro-N1-[6-[(2-bromo-2,3-dihydro-1-oxo-1H-inden-4- yl)oxy]-3-pyridinyl]benzamide produced in Application Example 175 was dissolved in 6 mL of DMF. 0.18 g of potassium formate and 0.3 mL of water were added and stirred for 2 h at room temperature. The reaction solution was extracted with ethyl acetate, washed with saturated saline, and dried on anhydrous sodium sulfate. The solvent was distilled off under reduced pressure. The solid residue was washed with ethyl acetate to obtain 0.62 g of the title compound. Very light yellow powder.

[0235]

^{1}H−NMR (DMSO-d_6) δ ppm : 2.80
(dd, 1H), 3.42 (dd, 1H), 5.55 (dd,1H), 7.21 (d, 1
H), 7.52-7.63 (m, 3H), 7.84 (d, 1H), 7.95 (dd, 1
H), 8.22-8.28 (m, 2H), 8.36 (s, 1H), 8.48 (d, 1H),
10.58 (s, 1H).

Application Example 177

Production of 2-(4-tert-butylphenoxy)-3-(3,4-dichlorobenzoylamino)pyridine-N-oxide

164 mg of m-chloroperbenzoic acid was added to 5 mL of a methylene chloride solution of 200 mg of the N-[6-(4-tert-butylphenoxy)pyridin-3-yl]-3,4- dichlorobenzamide obtained in Application Example 4 and refluxed while heating for 10 h. The reaction solution was allowed to cool, and the crystals that precipitated were filtered out to obtain 40 mg of the title compound.

[0236]

MS m/e 431 (M^+) for $C_{22}H_{20}Cl_2N_2O_3$.

Application Example 178

The compound of Application Example 177 [sic; 178] was produced by the same method as in Application Example 177.

MS m/e 428 (M+) for C21H14Cl2N2O4.

Application Example 179

(Step 1) Production of ethyl 6-[(1-t-butyldimethylsilanyloxy-2,3-dihydro-1H-inden-4-yl)oxy]nicotinate

t-Butyl dimethylchlorosilane (3.59 g) and imidazole (1.84 g) were added to a DMF (40 mL) solution of ethyl 6-[(1-hydroxy-2,3-dihydro-1H-inden-4-yl)oxy]nicotinate (4.75) and stirred for 17 h at room temperature. The reaction solution was concentrated under reduced pressure. Diethyl ether was added, and the solution was washed with water, 2% citric acid, water, a saturated sodium bicarbonate aqueous solution, and saturated saline. After drying on magnesium sulfate, it was concentrated under reduced pressure. The residue obtained was refined by silica gel chromatography (hexane: ethyl acetate = 20:1) to obtain the title compound (5.62 g).

^{1}H-NMR ($CDCl_3$) δ ppm: 0.16 (s, 3H), 0.18 (s, 3H), 0.96 (s, 9H), 1.38 (t, 3H, J=7Hz), 1.89 (m, 1H), 2.45 (m, 2H), 2.78 (dd, 1H, J=14Hz, 9Hz), 4.37 (q, 2H, J=7Hz), 5.31 (t, 1H, J=7Hz), 6.90 (d, 1H, J=8.5Hz), 7.00 (d, 1H, J=7.5Hz), 7.22 (d, 1H, J=7.5Hz), 7.30 (d, 1H, J=7.5Hz), 8.25 (dd, 1H, J=8.5Hz, 2Hz), 8.80 (d, 1H, J=2Hz).

(Step 2) Production of {6-[(1-tert-butyldimethylsilanyloxy)-indan-4-yloxy]-pyridin-3-yl}-methanol

A diethyl ether (10 mL) suspension of lithium aluminum hydride was cooled and a diethyl ether (8 mL) solution of ethyl 6-[(1-t-butyldimethylsilanyloxy-2,3-dihydro-1H-inden-4-yl)oxy]nicotinate (1.0 g) was added dropwise. After stirring for 20 min while cooling, water (100 μL), 1N NaOH (100 μL), and water (300 μL) were added sequentially followed by stirring for 20 min at room temperature. The insoluble matter was filtered out, and the filtrate was concentrated under reduced pressure to obtain the title compound (810 mg).

dissolved in 6 mL of DMF. 0.18

^{1}H-NMR ($CDCl_3$) δppm: 0.15 (s, 3H), 0.18 (s, 3H), 0.96 (s, 9H), 1.90 (m, 1H), 2.50 (m, 2H), 2.81 (dd, 1H, J=16Hz, 9Hz), 4.65 (s, 2H), 5.30 (t, 1H, J=7Hz), 6.87 (d, 1H, J=8Hz), 6.97 (d, 1H, J=8Hz), 7.19 (d, 1H, J=8Hz), 7.28 (d, 1H, J=8Hz), 7.71 (dd, 1H, J=8, 2H), 8.13 (d, 1H, J=2Hz).

(Step 3) Production of 2-[(1-tert-butyldimethylsilanyloxy)-indan-4-yloxy]-5-(4-trifluoromethylphenoxymethyl)pyridine

A toluene solution (1.1 mL) of 40% diethyl azodicarboxylate was added dropwise to a tetrahydrofuran (20 mL) solution of triphenyl phosphine (660 mg). After stirring for 15 min at room temperature, it was cooled to -20°C. A mixed tetrahydrofuran (15 mL) solution of {6-[(1-tert-butyldimethylsilanyloxy)indan-4-yloxy]-pyridin-3-yl}methanol and 4-hydroxybenzotrifluoride (205 mg) was added dropwise to the reaction solution and stirred for 17 h at room temperature. The reaction solution was concentrated under reduced pressure. The residue obtained was refined by silica gel chromatography (hexane: ethyl acetate = 10:1) to obtain the title compound (150 mg).

^{1}H-NMR ($CDCl_3$) δppm: 0.16 (s, 3H), 0.18 (s, 3H), 0.96 (s, 9H), 1.90 (m, 1H), 2.50 (m, 2H), 2.82 (dd, 1H, J=16, 9Hz), 5.03 (s, 2H), 5.31 (t, 1H, J=7Hz), 6.91 (d, 1H, J=8Hz), 6.99 (d, 1H, J=8Hz), 7.02 (d, 2H, J=9Hz), 7.20 (d, 2H, J=8Hz), 7.29 (t, 1H, J=8Hz), 7.56 (d, 2H, J=9H), 7.76 (dd, 1H, J=8, 2Hz), 8.21 (d, 1H, J=2Hz).

(Step 4) A tetrahydrofuran solution (590 mL) of 1N tetrabutylammonium fluoride was added to a tetrahydrofuran (3 mL) solution of 2-[(1-tert-butyl-dimethyl-silanyloxy)-indan-4-yloxy]-5-(4-trifluoromethylphenoxymethyl)pyridine and stirred for 5 h at room temperature. The reaction solution was concentrated under reduced pressure. Ethyl acetate was added, and the solution was washed with 1N hydrochloric acid, a saturated sodium bicarbonate aqueous solution, and saturated saline, dried on magnesium sulfate, and concentrated under reduced

pressure. The residue obtained was refined by silica gel chromatography (hexane: ethyl acetate = 1:1) to obtain the title compound (target compound) (90 mg).

^{1}H-NMR (DMSO-d_6) δ ppm: 1.75 (m, 1H), 2.20-2.80 (m, 3H), 5.09 (t, 1H, J=7Hz), 5.16 (s, 2H), 6.96 (dd, 1H, J=7.2Hz), 7.05 (d, 1H, J=9Hz), 7.21 (d, 2H, J=9Hz), 7.25 (m, 2H), 7.68 (d, 2H, J=9Hz), 7.95 (dd, 1H, J=9Hz, 2Hz), 8.23 (d, 1H, J=2Hz).

Application Example 180

Production of 2-(4-acetyl)phenoxy-5-(3,4-dichlorocinnamoyl)pyridine

(Step 1) Production of 4-benzyloxyacetophenone

The title compound was obtained in the same way as in Reference Example 1 using 4-hydroxyacetophenone and benzyl bromide.

^{1}H-NMR ($CDCl_3$) δ ppm: 2.56 (s, 3H), 5.14 (s, 2H), 7.01 (d, 2H), 7.34-7.45 (m, 5H), 7.94 (d, 2H).

(Step 2) Production of 4-benzyloxyacetophenone ethylene ketal

2.26 g of the 4-benzyloxyacetophenone produced in Step 1 were dissolved in 25 mL of benzene, and 0.67 mL of ethylene glycol and 23 mg of (() [sic]-10-camphor sulfonate were added. The solution was placed in a Dean-Stark apparatus, refluxed while heating, and stirred for 24 h. The reaction solution was concentrated under reduced pressure and extracted with ethyl acetate. The organic layer was washed with saturated sodium bicarbonate aqueous solution and saturated saline and dried on anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was refined by silica gel column chromatography (eluent: ethyl acetate: hexane = 1:5) to obtain 770 mg of the title compound. White powder.

[0237]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.65 (s, 3H), 3.75-3.80 (m, 2H), 4.00-4.05 (m, 2H), 5.06 (s, 2H), 6.94 (d, 2H), 7.32-7.45 (m, 7H).

(Step 3) Production of 4-hydroxyacetophenone ethylene ketal

2.05 g of the 4-benzyloxyacetophenone ethylene ketal produced in Step 2 was dissolved in a mixed solution of 100 mL of THF and 50 mL of methanol and catalytically reduced at room temperature in the presence of 0.8 g of 5% palladium-carbon. After 4 h, the catalyst was filtered

out. The filtrate was concentrated under reduced pressure and 1.38 g of the title compound was obtained. White, crystalline powder.

[0238]

^{1}H−NMR ($CDCl_3$) δ ppm : 1.68 (s, 3H), 3.76-3.81 (m, 2H), 4.01-4.06 (m, 2H), 5.09 (s, 1H), 6.79 (d, 2H), 7.35 (d, 2H).

(Step 4) Production of 5-acetyl-2-chloropyridine

35 mL of methyl lithium (1.1M ether solution) were added while cooling to 50 mL of a THF solution of 1.58 g of 6-chloronicotinic acid in an argon gas atmosphere. After stirring for 3 h at the same temperature, 25 mL of chlorotrimethylsilane were added and stirred for 30 min while gradually returning to room temperature. 1N Hydrochloric acid was added to the reaction solution, and the solution was extracted with ethyl acetate. The organic layer was washed with saturated saline and dried on anhydrous magnesium sulfate. The solvent [sic] was concentrated under reduced pressure. The residue was refined by silica gel column chromatography (eluent: ethyl acetate: hexane = 1:5) to obtain 280 mg of the title compound.

[0239]

^{1}H−NMR ($CDCl_3$) δ ppm : 2.64 (s, 3H), 7.46 (d, 1H, J = 8.3 Hz), 8.20 (dd, 1H, J = 2.3 Hz), 8.94 (d, 1H, J = 2.6Hz).

(Step 5) Production of 2-[4-(2-methyl-1,3-dioxolan-2-yl)phenoxy]-5-acetylpyridine

The title compound was obtained in the same way as in Reference Example 1 using the 4-hydroxyacetophenone ethylene ketal produced in Step 3 and the 5-acetyl-1-chloropyridine produced in Step 4.

^{1}H−NMR ($CDCl_3$) δ ppm : 1.68 (s, 3H), 2.57 (s, 3H), 3.80-3.85 (m, 2H), 4.04-4.09 (m, 2H), 6.98 (d, 1H), 7.14 (d, 2H), 7.54 (d, 2H), 8.27 (dd, 1H), 8.77 (d, 1H).

(Step 6) Production of 2-[4-(2-methyl-1,3-dioxolan-2-yl)phenoxy]-5-(3,4-dichlorocinnamoyl)pyridine

400 mg of the 2-[4-(2-methyl-1,3-dioxolan-2-yl)phenoxy]-5-acetyl pyridine produced in Step 5 and 234 mg of 3,4-dichlorobenzaldehyde were added to 4 mL of a methanol solution of 11 mg of 60% sodium hydride and stirred for 20 h at room temperature. The solid that precipitated was filtered out and refined by silica gel column chromatography (eluent: ethyl acetate: hexane = 1:5) to obtain 370 mg of the title compound. White powder.

[0240]

^{1}H−NMR ($CDCl_3$) δ ppm : 1.69 (s, 3H), 3.80-3.86 (m, 2H), 4.04-4.09 (m, 2H), 7.03 (d, 1H), 7.14 (d, 2H), 7.39-7.52 (m, 3H), 7.55 (d, 2H), 7.68-7.74 (m, 2H), 8.34 (dd, 1H), 8.86 (d, 1H).

(Step 7) Production of 2-(4-acetyl)phenoxy-5-(3,4-dichlorocinnamoyl)pyridine

370 mg of the 2-[4-(2-methyl-1,3-dioxolan-2-yl)phenoxy]-5- (3,4-dichlorocinnamoyl)pyridine produced in Step 6 were dissolved in 4 mL of THF, and 2 mL of 1N HCl were added and stirred at room temperature. After 2 h, the mixture was extracted with ethyl acetate. The organic layer was washed with saturated saline and dried on anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The crystals produced by adding ether were filtered out to obtain 280 mg of the title compound (target compound). White powder.

[0241]

^{1}H−NMR ($CDCl_3$) δ ppm : 2.63 (s, 3H), 7.11 (d, 1H), 7.27 (d, 2H), 7.42-7.53 (m, 3H), 7.70-7.75 (m, 2H), 8.06 (d, 2H), 8.38 (dd, 1H), 8.85 (d, 1H).

The compounds of Application Examples 181-185 below were produced by the same method as in Application Example 180.

<u>Application Example 181</u>

^{1}H−NMR (CDC13) δ ppm : 2.42 (s, 3H), 3.99 (s, 6H), 6.94 (d, 1H), 6.97 (d, 1H), 7.28 (d, 2H), 7.43 (d, 2H), 7.57 (s, 1H), 7.63 (d, 2H), 7.73 (dd, 1H), 8.20 (d, 1H), 8.48 (d, 1H).

<u>Application Example 182</u>

^{1}H−NMR (DMSO-d_6) δ ppm : 2.38 (s, 3H), 3.78 (s, 3H), 3.91 (s, 6H), 7.02 (d, 1H), 7.37 (d, 2H), 7.49-7.51 (m, 4H), 8.02-8.18 (m, 3H), 8.76 (d, 1H).

<u>Application Example 183</u>

MS m/e 444 (M+).

Application Example 184

^{1}H−NMR ($CDCl_3$) δ ppm : 1.68 (s, 3H), 3.79-3.83 (m, 2H), 4.02-4.10(m, 2H), 7.04 (dd, 1H), 7.12-7.17 (m, 2H), 7.47-7.58 (m, 3H), 7.66-7.74(m, 4H), 7.83 (d, 1H), 8.38 (dd, 1H), 8.88 (d, 1H).

Application Example 185

Production of E-1-[6-(3,4-methylenedioxyphenoxy)pyridin-3-yl]-2-[4-(trifluoromethyl)phenyl]ethene

1.20 g of (4-trifluorophenyl)benzyltriphenylphosphonium bromide and 0.27 g of potassium t-butoxide were added while cooling to 5 mL of a dichloromethane solution of 0.58 g of 3-formyl-6-(3,4-methylenedioxyphenoxy)pyridine. The reaction solution was stirred for 2 days while gradually returning to room temperature. After adding dichloromethane and water to the reaction solution, the organic layer was washed with water, a saturated sodium bicarbonate aqueous solution, and saturated saline and dried by anhydrous magnesium sulfate. The solvent was distilled off. The residue was refined by a silica gel column (eluent: hexane/ethyl acetate = 5/1) to obtain 70 mg of the title compound.

^{1}H−NMR ($CDCl_3$) δ ppm : 6.01(s, 2H), 6.62 (dd, 1H, J = 2 Hz, 9 Hz), 6.68 (d, 1H, J = 2 Hz), 6.82 (d, 1H, J = 9 Hz), 6.92 (d, 1H, J = 9 Hz), 7.00 (d, 1H, J = 17 Hz), 7.13 (d, 1H, J = 17 Hz), 7.59-7.62 (m, 4H), 7.90 (dd, 1H, J = 2 Hz, 9 Hz), 8.28 (d, 1H, J = 2 Hz).

The compounds of Application Examples 186-191 below were produced by the same method as in Application Example 185.

[0242]

Application Example 186

^{1}H−NMR ($CDCl_3$) δ ppm : 6.43 (d, 1H, J = 12.2 Hz), 6.63 (d, 1H, J= 12.2 Hz),6.86-6.90 (m, 2H), 7.00-7.04 (m, 2H), 7.06-7.15 (m, 2H), 7.16-7.19 (m, 2H), 7.26-7.37 (m, 4H).

Application Example 187

^{1}H−NMR ($CDCl_3$) δ ppm : 7.00-7.06 (m, 5H), 7.10-7.26 (m, 2H), 7.32-7.39 (m, 2H), 7.47-7.52 (m, 2H), 7.56-7.63 (m, 4H).

Application Example 188

^{1}H−NMR ($CDCl_3$) δ ppm : 6.55 (d, 1H, J = 12 Hz), 6.66 (d, 1H, J =12 Hz), 6.85-6.89 (m, 2H), 7.01-7.04 (m, 2H), 7.07-7.15 (m, 1H), 7.16-7.19 (m, 2H), 7.32-7.38 (m, 4H), 7.47-7.50 (m, 2H).

Application Example 189

^{1}H−NMR ($CDCl_3$) δ ppm : 6.43 (d, 1H, J = 12 Hz), 6.63 (d, 1H, J =12 Hz), 6.86-6.90 (m, 2H), 7.00-7.04 (m, 2H), 7.06-7.15 (m, 2H), 7.16-7.19 (m, 2H), 7.32-7.37 (m, 4H).

Application Example 190

^{1}H−NMR ($CDCl_3$) δ ppm : 1.66 (s, 3H), 3.77-3.86 (m, 2H), 3.98-4.13(m, 2H), 6.55 (d, 1H, J = 12 Hz), 6.68 (d, 1H, J = 12 Hz), 6.84-6.90 (m, 2H), 6.94-7.00 (m, 2H), 7.15-7.20 (m, 2H), 7.35-7.38 (m, 2H), 7.42-7.50 (m, 4H).

Application Example 191

^{1}H−NMR ($CDCl_3$) δ ppm : 1.66 (s, 3H), 3.78-3.83 (m, 2H), 4.02-4.07(m, 2H), 6.44 (d, 1H, J = 12 Hz), 6.63 (d, 1H, J = 12 Hz), 6.87-6.91 (m, 2H), 6.94-7.00 (m, 2H), 7.06-7.10 (m, 1H), 7.15-7.19 (m, 2H), 7.29 (d,1H, J = 8 Hz), 7.33 (d, 1H, J = 2 Hz), 7.42-7.47 (m, 2H).

Application Example 192

Iodomethane (68 mL) and 1,8-diazabicyclo[5.4.0]-7-undecene (18 mL) were added to an N1-{6-[(1-oxo)-2,3-dihydro-1H-inden-4-yl]oxy]pyridin-3-yl}-N3-(3,4-dichlorophenyl)thiourea (49 mg) solution and stirred for 3 h at 50°C. The reaction solution was concentrated under reduced pressure. Ethyl acetate was added, and the solution was washed with water and saturated saline. The organic layer was dried on magnesium sulfate, then concentrated under reduced pressure. An ethanol solution of ammonia was added to the residue obtained, which was then heated for 8 h at 100°C in a sealed tube. The reaction solution was concentrated under reduced pressure. The residue obtained was refined by silica gel chromatography (chloroform: methanol = 4:1) to obtain the title compound (3 mg).

^{1}H-NMR ($CDCl_3$) δ ppm: 2.64 (t, 2H, J=6Hz), 2.88 (t, 2H, J=6Hz), 6.30 (brs, 1H), 7.10 (d, 1H, J=9Hz), 7.20 (brs, 1H), 7.35-7.80 (m, 6H), 7.96 (brs, 1H), 9.50 (brs, 1H).

Application Example 193

Production of 3-(5-nitro-2-p-tolylsulfinylphenyl)-1-(3,4,5-trimethoxyphenyl)propenone

10 drops of 30% hydrogen peroxide were added to 5 mL of an acetic acid solution of 100 mg of the 3-(5-nitro-2-p-tolylsulfanylphenyl)-1-(3,4,5-trimethoxyphenyl)propenone obtained in Application Example 2. The reaction solution was stirred overnight at room temperature. Water and ether were added to the reaction solution. The ether layer was separated and washed with water. The solvent was distilled off after drying on anhydrous magnesium sulfate. The residue was washed with ether to obtain 30 mg of the title compound.

[0243]

^{1}H-NMR ($CDCl_3$) δ ppm: 2.32 (s, 3H), 3.97 (s, 9H), 7.20-7.27 (m, 4H), 7.46 (d, 1H), 7.54 (d, 2H), 8.13 (d, 1H), 8.44-8.50 (m, 3H).

Application Example 194

^{1}H-NMR ($CDCl_3$) δ ppm: 1.29 (s, 9H), 3.93 (s, 6H), 6.88 (d, 1H, J = 8.3 Hz), 7.42-7.48 (m, 4H), 7.64-7.67 (m, 2H), 7.97 (d, 1H, J = 8.6 Hz), 8.34 (dd, 1H, J = 2.6 Hz, 8.6 Hz), 8.37 (brs, 1H), 8.79 (d, 1H, J = 2.6 Hz).

Application Example 195

Production of 3-(5-nitro-2-p-tolylsulfonylphenyl)-1-(3,4,5-trimethoxyphenyl)propenone

130 mg of 30% aqueous hydrogen peroxide were added to 10 mL of an acetic acid solution of 268 mg of the 3-(5-nitro-2-p-tolylsulfanylphenyl)-1-(3,4,5-trimethoxyphenyl)propenone obtained in Application Example 183. The reaction solution was stirred for one day at room temperature. The reaction solution was concentrated under reduced pressure. Water and ethyl acetate were added to the residue. The organic layer was separated and washed with water. The solvent was distilled off after drying on anhydrous magnesium sulfate.

The residue was refined by silica gel column chromatography (eluent: n-hexane/ethyl acetate = 1/1) to obtain 50 mg of the title compound.

[0244]

^{1}H-NMR ($CDCl_3$) δ ppm : 2.35 (s, 3H), 3.95 (s, 9H), 7.19-7.27(m, 5H), 7.75 (d, 2H), 8.33-8.47 (m, 4H).

Application Example 196

The compound of Application Example 196 was produced by the same method as in Application Example 195.

^{1}H-NMR ($CDCl_3$) δ ppm : 132 (s, 9H), 3.95 (s, 6H), 6.91 (d, 1H, J = 8.3 Hz), 7.43-7.54 (m, 4H), 7.93-7.97 (m, 2H), 8.16 (d, 1H, J = 8.6 Hz), 8.17 (brs, 1H), 8.48 (dd, 1H, J = 2.6 Hz, 8.6 Hz), 8.71 (d, 1H, J = 2.6 Hz).

Application Example 197

Celite (450 mg) and pyridinium chlorochromate (200 mg) were added to a dichloromethane (14 mL) solution of 1-{6-[1-hydroxyindan-4-yloxy]-pyridin-3-yl}-2-(3,4-dichlorophenyl)ethanone (190 mg) and stirred for 40 min at room temperature. The reaction solution was filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue obtained was refined by silica gel chromatography (hexane: ethyl acetate = 2:1) to obtain the title compound (150 mg).

^{1}H-NMR (DMSO-d_6) δ ppm : 2.65 (t, 2H, J=5Hz), 2.85 (t, 2H, J=5Hz), 4.45 (s, 2H), 7.26 (d, 1H, J=9Hz), 7.30 (d, 1H, J=9Hz), 7.57 (m, 5H), 8.43 (dd, 1H, J=9, 2Hz), 8.86 (s, 1H).

Application Example 198

Production of 2-carboxy-4,5-dichloro-N1-[6-[(1-oxo-2,3-dihydro-1H-inden-4-yl)oxy]-3-pyridinyl]benzamide

0.22 g of 4-[(5-amino-2-pyridinyl)oxy]-1-indanone produced in the same way as in Reference Example 2 was dissolved in 10 mL of tetrahydrofuran, and 0.22 g of anhydrous 4,5-dichlorophthalic acid and 0.13 mL of triethylamine were added and stirred for 20 h at room

temperature. The reaction solution was dissolved in a mixed solution of 20 mL of tetrahydrofuran and 50 mL of ethyl acetate and washed with 5% citric acid aqueous solution followed by saturated saline. After drying on anhydrous sodium sulfate, the solvent was distilled off under reduced pressure. The solid residue was recrystallized from a mixed solution of methanol-ethyl acetate-hexane to obtain 0.16 g of the title compound. White powder.

[0245]

^{1}H−NMR (DMSO-d_6) δ ppm : 2.62-2.67 (m, 2H), 2.84-2.88 (m, 2H), 7.19 (d, 1H, J = 8.9 Hz), 7.42-7.46 (m, 1H), 7.49-7.52 (m, 2H), 7.96 (s, 1H), 8.06 (s, 1H), 8.18 (dd, 1H, J = 2.6 Hz, 8.9 Hz), 8.35 (d, 1H, J = 2.3 Hz), 10.65 (s, 1H).

Application Example 199

Production of N-acetyl-N-(3,4-dichlorophenyl)-6-[(3-acetoxy-1H-inden-7-yl)oxy]nicotinamide

250 mg of p-toluenesulfonic acid monohydrate and 5 mL of isopropenyl acetate were added to 490 mg of N-(3,4-dichlorophenyl)-6-[(2,3-dihydro-1-oxo-1H- inden-4-yl)oxy]nicotinamide. The reaction mixture was stirred for 30 min at 80°C. The reaction solution was concentrated under reduced pressure, and ethyl acetate and saturated sodium bicarbonate aqueous solution were added to the residue. The organic layer was separated, washed with saturated sodium bicarbonate aqueous solution and water, and dried by anhydrous magnesium sulfate. The solvent was distilled off. The residue was refined by silica gel column chromatography (eluent: n-hexane/ethyl acetate = 2/1) to obtain 330 mg of the title compound.

[0246]

^{1}H−NMR ($CDCl_3$) δ ppm : 2.34 (s, 3H), 2.40 (s, 3H), 3.20 (d, 2H, J = 2 Hz), 6.32 (t, 1H, J = 2 Hz), 6.91-7.03 (m, 3H), 7.22-7.41 (m, 3H), 7.45 (d, 1H, J = 9 Hz), 7.95 (dd, 1H, J = 2 Hz, 9 Hz), 8.38 (d, 1H, J =2 Hz).

Application Example 200

Celite (120 mg) and pyridinium chlorochromate (95 mg) were added to a dichloromethane (3 mL) solution of 4-{[5-(4-trifluoromethylphenoxymethyl)pyridin-2-yl]oxy}indan-1-ol (88 mg) and stirred for 20 min at room temperature. The reaction solution was

filtered through Celite, and the filtrate was concentrated under reduced pressure. The residue obtained was refined by silica gel chromatography (hexane: ethyl acetate = 2:1) to obtain the title compound (56 mg).

^{1}H-NMR ($CDCl_3$) δ ppm: 2.69 (t, 2H, J=6Hz), 2.97 (t, 2H, J=6Hz), 5.06 (s, 2H), 7.03 (d, 2H, J=9Hz), 7.07 (d, 1H, J=8Hz), 7.10 (d, 1H, J=9Hz), 7.45 (t, 1H, J=8Hz), 7.58 (d, 2H, J=9Hz), 7.67 (d, 1H, J=8Hz), 7.84 (dd, 1H, J=9Hz, 2Hz), 8.20 (d, 1H, J=2Hz).

Application Example 201

Production of N1-[6-(4-acetylphenoxy)-3-pyridinyl]-N1-methyl-3,4-dichlorobenzamide

(Step 1) Production of 1-[4-[(5-methylamino-2-pyridinyl)oxy]phenyl]-1-ethanone

1.14 g of 1-[4-[(5-amino-2-pyridinyl)oxy]phenyl]-1-ethanone produced in the same way as in Reference Example 2 was dissolved in a mixed solution of 5 mL of benzene and 10 mL of tetrahydrofuran, and 32 mg of tetrabutylammonium bromide, 0.8 g of sodium hydroxide, and 0.7 g of anhydrous potassium carbonate were added. After stirring for 1 h at 40°C, 0.5 mL of dimethyl sulfate was added, and stirring was continued for 6 h at 50°C and for two days at room temperature. The reaction solution was extracted with ethyl acetate, washed with water, and dried on anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure. The residue was refined by silica gel column chromatography (eluent: chloroform: methanol = 60:1) to obtain 0.2 g of the title compound. Light brown oil.

^{1}H-NMR ($CDCl_3$) δ ppm: 2.57 (s, 3H), 2.87 (s, 3H), 3.76 (brs, 1H), 6.87 (d, 1H), 7.01-7.08 (m, 3H), 7.67 (d, 1H), 7.95 (d, 2H).

(Step 2) Production of N1-[6-(4-acetylphenoxy)-3-pyridinyl]-N1-methyl-3,4-dichlorobenzamide

The title compound (target compound) was obtained in the same way as in Application Example 88 using the 1-[4-[(5-methylamino-2-pyridinyl)oxy]phenyl]-1-ethanone produced in Step 1 and 3,4-dichlorobenzoyl chloride. White powder.

[0247]

^{1}H−NMR (DMSO-d_6) δ ppm : 2.57 (s, 3H), 3.40 (s, 3H), 7.12-7.17 (m, 3H), 7.23-7.26 (m, 1H), 7.56-7.59 (m, 2H), 7.88 (dd, 1H), 7.99 (d, 2H), 8.05 (d, 1H).

Application Example 202

The compounds of Application Examples 202 and 203 were produced by the same method as in Application Example 201.

^{1}H−NMR (DMSO-d_6) δ ppm : 2.56 (s, 3H), 3.39 (s, 3H), 7.09-7.15 (m, 3H), 7.49-7.53 (m, 2H), 7.68 (d, 2H), 7.91 (dd, 1H), 7.98-8.02 (m, 3H).

Application Example 203

^{1}H−NMR ($CDCl_3$) δ ppm : 2.63-2.68 (m, 2H), 2.78-2.83 (m, 2H), 3.47(s, 3H), 7.00 (d, 1H), 7.13 (dd, 1H), 7.27-7.36 (m, 3H), 7.41-7.46 (m,1H), 7.53 (dd, 1H), 7.65 (dd, 1H), 7.78 (d, 1H).

Application Example 204

Production of N1-(4-hydroxyphenyl)-N3-[6-((1-oxo-2,3-dihydro-1H-inden-4-yl)oxy)pyridin-3-yl] urea

5 mL of 48% hydrobromic acid were added to 200 mg of the N1-(4- methoxyphenyl)-N3-[6-((1-oxo-2,3-dihydro-1H-inden-4-yl)oxy)pyridin-3-yl] urea obtained in Application Example 114 and stirred for 5 h at 100°C. The reaction solution was concentrated under reduced pressure, and ethyl acetate and water were added to the residue. The ethyl acetate layer was separated and washed with water. The solvent was distilled off after drying on anhydrous magnesium sulfate. The residue was refined by silica gel column chromatography (eluent: n-hexane/ethyl acetate = 1/1) to obtain 50 mg of the title compound.

[0248]

^{1}H−NMR (DMSO-d_6) δ ppm : 2.61-2.66 (m, 2H), 2.84-2.88 (m, 2H), 6.67-6.70 (m, 2H), 7.09 (d, 1H), 7.17-7.22 (m, 2H), 7.37-7.49 (m, 3H), 8.02 (dd, 1H), 8.15 (d, 1H), 8.43 (brs, 1H), 8.66 (brs, 1H), 9.08 (s, 1H).

Application Example 205

The compound of Application Example 205 was produced by the same method as in Application Example 204.

^{1}H−NMR (DMSO-d_6) δ ppm:
6.90 (tt, 1 H, J=2 Hz, 7 Hz), 7.07 (d, 1H, J=9 H
z), 7.17 (d, 1 H, J=7 Hz), 7.24-7.36 (m, 3 H), 7.4
3 (t, 1 H, J=9 Hz), 7.51 (d, 1 H, J=9 Hz), 7.86
(d, 1 H, J=3 Hz), 7.99 (m, 2 H), 8.11(d, 1 H, J=3
Hz), 8.86 (s, 1 H), 9.08 (s, 1 H), 10.23 (s, 1 H).

Application Example 206

Production of 3,4-dichloro-N-{[4-(1-hydroxyindan-4-yl)oxy]phenyl}benzamide

6 mg of sodium borohydride were added to 1.25 mL of a THF-water (4:1) solution of 100 mg of the 3,4-dichloro-N-{[4-(1-oxoindan-4-yl)oxy]phenyl}benzamide obtained in Application Example 34 and stirred for 2.5 h at room temperature. The reaction solution was concentrated under reduced pressure, and ethyl acetate and water were added to the residue. The organic layer was separated, washed with water, and dried on anhydrous magnesium sulfate. The solvent was distilled off, and the residue was refined by silica gel column chromatography to obtain 90 mg of the title compound.

^{1}H−NMR (DMSO-d_6) δ ppm: 1.76-1.81 (m, 1H).
2.30-2.36 (m, 2H), 2.74-2.79 (m, 1H), 5.05-5.09
(m, 1H), 5.30 (d, 1H), 6.78 (d, 1H), 6.94-6.99 (m,
2H), 7.14-7.26 (m, 2H), 7.70-7.76 (m, 2H), 7.82
(d, 1H), 7.93 (dd,1H), 8.21 (d, 1H), 10.39 (s, 1
H).

The compounds of Application Examples 207 and 208 below were produced by the same method as in Application Example 206.

[0249]

Application Example 207

^{1}H−NMR ($CDCl_3$) δ ppm: 1.77-2.04 (m, 4H),
2.68-2.76 (m, 2H), 4.77-4.80 (m, 1H), 6.73 (d, 1
H), 6.85 (dd, 1H), 7.01-7.06 (m, 2H), 7.40 (d,1H),
7.55-7.59 (m, 3H), 7.70 (dd, 1H), 7.97 (d, 1H).

Application Example 208

^{1}H-NMR ($CDCl_3$) δ ppm: 1.72-2.06 (m, 5H), 2.65-2.87 (m, 2H), 4.73 (t, 1H), 6.87 (dd, 1H), 7.00-7.10 (m, 4H), 7.53-7.59 (m, 3H), 7.70 (dd, 1H), 7.76 (s, 1H), 7.97 (d, 1H).

Application Example 209

Production of 3,4-dichloro-N-[[6-(3-hydroxyphenyl)oxy]pyridin-3-yl]benzamide

2 mL of 1N sodium hydroxide aqueous solution were added while cooling to 15 mL of a THF solution of 600 mg of the N-[[6-(3-acetyloxyphenyl)oxy]pyridin-3-yl]-3,4-dichlorobenzamide obtained in Application Example 87 and stirred for 5 h at room temperature. Water was added to the reaction solution while cooling. The solution was acidified with 10% hydrochloric acid, and then extracted with ethyl acetate. The ethyl acetate extract was washed with water and dried on anhydrous magnesium sulfate. The solvent was distilled off, and the residue was recrystallized from ethyl acetate to obtain 460 mg of the title compound.

[0250]

^{1}H-NMR (DMSO-d_6) δ ppm: 6.46-6.53 (m, 2H), 6.57-6.62 (m, 1H), 7.04 (d, 1H, J = 8.9 Hz), 7.15-7.21 (m, 1H), 7.84 (d, 1H, J = 8.2 Hz), 7.93-7.97 (m, 1H), 8.17-8.23 (m, 2H), 8.51-8.52 (m, 1H), 9.60 (brs, 1H), 10.55 (brs, 1H).

The compounds of Application Examples 210 and 211 below were produced by the same method as in Application Example 209.

[0251]

Application Example 210

^{1}H-NMR (DMSO-d_6) δ ppm: 7.17 (d, 1H, J = 9 Hz), 7.38-7.43 (m, 1H), 7.53-7.59 (m, 2H), 7.76-7.86 (m, 2H), 7.93-7.97 (m, 1H), 8.22-8.27 (m, 2H), 8.51 (d, 1H, J = 2 Hz), 10.60 (s, 1H), 13.15 (brs, 1H).

Application Example 211

^{1}H−NMR (DMSO-d_6) δ ppm : 6.47-6.54 (m, 2H), 6.58-6.62 (m, 1H), 7.03-7.07 (m, 1H), 7.15-7.21 (m, 1H), 7.93-7.96 (m, 2H), 8.16-8.19 (m, 2H), 8.20-8.24 (m, 1H), 8.54 (d, 1H, J = 2.3 Hz), 9.62 (s, 1H), 10.65 (s, 1H).

Application Example 212

Production of 3,4-dichloro-N-[6-(3-hydroxymethylphenoxy)pyridin-3-yl]benzamide

10 mL of a THF solution of 500 mg of 3,4-dichloro-N-[6-(3-methoxycarbonylphenoxy)pyridin-3-yl]benzamide were added dropwise to 10 mL of a THF suspension of 180 mg of lithium aluminum hydride while cooling. The reaction solution was stirred for 1 h at room temperature. Saturated sodium sulfate aqueous solution and ethyl acetate were added to the reaction solution. The organic layer was separated, washed with water, and dried on anhydrous sodium sulfate. The solvent was distilled off, and the residue was recrystallized from ethyl acetate-hexane to obtain 300 mg of the title compound.

[0252]

^{1}H−NMR (DMSO-d_6) δ ppm : 4.51 (d, 2H), 5.25 (t, 1H), 6.98 (d, 1H), 7.04-7.15 (m, 3H), 7.36 (t, 1H), 7.84 (d, 1H), 7.93-7.97 (m, 1H), 8.18 (d, 1H), 8.22 (m, 1H), 8.49 (d, 1H), 10.56 (s, 1H).

Application Example 213

1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (140 mg) was added to an N,N-dimethylformamide (4 mL) solution of 6-[4-(2-oxopropyl)phenoxy]nicotinic acid (160 mg) and 3,4-dichloroaniline (105 mg) and stirred for one day at room temperature. The reaction solution was concentrated under reduced pressure. Ethyl acetate was added, and the solution was washed with water, saturated sodium bicarbonate aqueous solution, and saturated saline. After drying on magnesium sulfate, it was concentrated under reduced pressure, and the residue obtained was refined by silica gel chromatography (chloroform) to obtain the title compound (60 mg).

^{1}H−NMR ($CDCl_3$) δ ppm : 2.20 (s, 3H), 3.74 (s, 2H), 7.03 (d, 1H, J= 9 Hz), 7.13 (d, 2H, J = 8.5 Hz), 7.27 (d, 2H, J = 8.5 Hz), 7.43 (s, 2H), 7.80 (s, 1H), 7.87 (s, 1H), 8.19 (dd, 1H, J = 9 Hz, 2.5 Hz), 8.63 (d, 1H, J = 2.5 Hz).

The compounds of Application Example 214-217 below were produced by the same method as in Application Example 213.

[0253]

Application Example 214

^{1}H−NMR ($CDCl_3$) δ ppm : 1.39 (s, 3 H), 2.00 (m, 2 H), 2.75 (m, 2 H), 3.99 (m, 4 H), 6.99 (d, 1 H, J=9 Hz), 7.07 (d, 2 H, J=8 Hz), 7.26 (d,2 H, J =8 Hz), 7.42 (s, 2 H), 7.69 (s, 1 H), 7.87 (s, 1 H), 8.17 (dd, 1H, J=2 Hz, 9 Hz), 8.64 (d, 1 H, J=2 Hz).

Application Example 215

^{1}H−NMR ($CDCl_3$) δ ppm : 2.22 (s, 3H), 3.75 (s, 2H), 7.05 (d, 1H, J= 8.5 Hz), 7.14 (d, 2H, J = 8.5 Hz), 7.28 (d, 2H, J = 8.5 Hz), 7.64 (d,2H, J = 8.5 Hz), 7.76 (d, 2H, J = 8.5 Hz), 7.87 (s, 1H), 8.23 (dd, 1H,J = 8.5 Hz, 2.5 Hz), 8.67 (d, 1H, J = 2.5 Hz).

Application Example 216

^{1}H−NMR ($CDCl_3$) δ ppm : 1.85 (s, 3 H), 2.26 (m, 2 H), 2.90 (m, 2 H), 3.38 (m, 4 H), 7.01 (d, 1 H, J=9 Hz), 7.07 (d, 2 H, J=9 Hz), 7.27 (d,2 H, J =9 Hz), 7.64 (d, 2 H, J=9 Hz),7.76 (d, 2 H, J=9 Hz), 7.82 (s, 1 H), 8.21 (dd, 1 H, J=2.5 Hz, 9 Hz), 8.67 (d, 1 H, J=2.5 Hz).

Application Example 217

^{1}H−NMR ($CDCl_3$) δ ppm : 1.85 (s, 3 H), 2.26 (m, 2 H), 2.90 (m, 2H), 3.38 (m, 4 H), 7.00 (d, 1 H, J=8.5 Hz), 7.07 (d, 2 H, J=8 Hz), 7.27(d, 2 H, J=8 Hz), 7.43 (s, 2 H), 7.71 (s, 1 H), 7.87 (s, 1 H), 8.18 (dd,1 H, J=2.5 Hz, 8.5 Hz), 8.65 (d, 1 H, J=2.5 Hz).

Application Example 218

^{1}H−NMR ($CDCl_3$) δ ppm : 2.30(s,3H), 2.32(s,3 H), 7.30 (d, 1 H, J=8 Hz), 7.74 (d,1 H,J=8Hz), 7.75 (s, 1 H), 7.88 (d, 1 H,J=8Hz), 8.00(dd,1H,J=8,2Hz),8.05(d,1H,J=9Hz),8.28(d,1H,J=2Hz),8.45(dd,1H,J=9.2Hz),9.05(d,1H,J=2Hz),10.93(s,1H).

Application Example 219

Production of 2-(3,4-methylenedioxyphenoxy)-5-[2-(4-trifluoromethylphenyl)ethyl]pyridine hydrochloride

10 mg of 5% palladium-carbon were added to 10 mL of a THF solution of 100 mg of the 2-(3,4-methylenedioxyphenoxy)-5-[2-(4-trifluoromethylphenyl)vinyl]pyridine obtained in Application Example 185 and stirred for 4 h at room temperature in a hydrogen stream. The catalyst was filtered out, and the solvent was distilled off. The residue was dissolved in 5 mL of 4N hydrochloric acid-ethyl acetate and allowed to stand for 30 min at room temperature. The reaction solution was concentrated, and the residue was crystallized by ether to obtain 50 mg of the title compound.

[0254]

^{1}H−NMR ($CDCl_3$) δ ppm : 2.88-2.95(m, 4H), 5.98 (s, 2H), 6.58 (dd, 1H), 6.65 (d, 1 H), 6.79 (d, 2H), 7.23-7.26 (m, 2H), 7.41 (dd, 1 H), 7.53(d, 2H), 7.97 (d, 1H).

Production Example 1

Compound of Application Example 207	100 g
Avicel (trade name, made by Asahi Kasei)	40 g
Corn starch	30 g
Magnesium stearate	2 g

TC-5 (trade name, made by Shin-etsu Chemical)
hydroxypropylmethylcellulose 10 g
Polyethylene glycol 6000 3 g
Castor oil 40 g
Ethanol q.s.

Sugar-coated tablets with a radius of 10 mm were made after mixing and grinding the compound obtained in Application Example 207, corn starch, and magnesium stearate. The tablets obtained were film-coated with a coating composed of TC-5, polyethylene glycol 6000, castor oil, and ethanol to produce film-coated tablets of the above composition.

[0255]

Film-coated tablets were produced in the same way as above using the compound of Application Example 127.

Test Example 1

The following collagen synthesis study was performed using the benzene derivatives of the present invention (test compounds).

[Collagen synthesis inhibition study]

(Preparation of plasma-derived serum (PDS)) Plasma obtained by centrifuging rabbit blood was again centrifuged to remove the platelets, and the supernatant obtained was dialyzed against phosphate-buffered saline (PBS) that contained 0.1% (w/v) calcium chloride and 0.1% (w/v) magnesium chloride. It was then centrifuged to remove the sediment that precipitated, and the supernatant obtained was immobilized for 30 min at 56°C. Plasma-derived serum (PDS) was prepared by sterilizing with a 0.22 μm filter.

(Measurement method) Human Ito cell-like cultured cells (L190) were sown on Dulbecco's modified Eagle medium (DMEM) that contained 10% fetal calf serum and cultured for 24 h in an incubator in the presence of carbon dioxide (CO2). They were then washed with the above PBS and cultured for 3 days in Eagle's minimum essential medium (MEM) that contained 2% PDS. The cultured cells were then washed with the above PBS and cultured for 16 h together with the test compound in MEM that contained 10 pMh TGF (transforming growth factor) β-1 (containing 2% PDS relative to the total amount of MEM). The cultured L190 were then washed with the above PBS and RI (radioisotope) labeled (labeled) for 24 h in MEM that contained 3H-proline, a radiolabel, and 0.25 mM ascorbic acid. After precipitating the cultured supernatant with trichloroacetic acid, the radioactivity in the acid-soluble fraction was measured, and the value obtained was taken as the collagen synthesis activity.

[0256]

The collagen synthesis-inhibiting activity (T/C) was calculated by comparing the radioactivity in the cultured supernatant that contained the test compound with the radioactivity in a cultured supernatant that did not contain any test compound (control). The concentration that inhibits collagen synthesis by 50% (μM) (concentration of test compound corresponding to an IC_{50} = T/C of 0.5) was determined. T/C was determined by the following formula.

T/C = (Radioactivity in culture supernatant containing test compound)/(radioactivity in control culture supernatant)

The test results are shown in Table 59.

[0257]

Table 59

	IC_{50} (μM)
実施例32	2.37
実施例34	2.01
実施例71	1.84
実施例72	2.44
実施例88	8.38
実施例92	8.23
実施例115	3.13
実施例116	4.03
実施例117	3.60
実施例118	7.74
実施例121	4.48
実施例125	4.07
実施例126	6.52
実施例134	7.55
実施例161	7.28
実施例167	2.66
実施例168	1.76
実施例193	7.30
実施例198	4.51
実施例200	6.23
実施例201	5.50

Key: 1 Application Example ___